# ABSTRACT eBOOK

# CROI 2022

## Conference on Retroviruses and Opportunistic Infections

February 12-16

with Symposia on February 22, 23, and 24



IAS–USA
International Antiviral Society–USA
Version 4 | Last Updated on February 17, 2022

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# ABSTRACT PROCESS

## Scientific Categories

### Basic Science

- **A.** Virology of HIV or SARS-CoV-2
- **B.** Pathogenesis of HIV or SARS-CoV-2: Human Studies and Animal Models
- **C.** HIV-Associated Tumor Viruses
- **D.** Host Immune Responses, Vaccines, and Immunotherapies: HIV or SARS-CoV-2
- **E.** HIV Reservoirs, Latency, and Curative Strategies, Including Therapeutic Vaccines and Gene Therapy
- **F.** Neuropathogenesis and Neurologic Complications of HIV, SARS-CoV-2, or Both in Adults

### Clinical

- **G.** Clinical Pharmacology in Adults
- **H.** Antiviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy, and Effectiveness Studies in HIV or SARS-CoV-2 in Adults
- **I.** Resistance of HIV or SARS-CoV-2 to Small Molecules and Antibodies in Adults
- **J.** Hepatitis Viruses and Liver Complications in Adults
- **K.** AIDS-Related Malignancies
- **L.** Cardiovascular Complications of HIV Infection and Antiretroviral Therapy
- **M.** Other Complications of HIV Infection and Antiretroviral Therapy in Adults
- **N.** Clinical Complications of COVID-19 Disease in Adults
- **O.** Tuberculosis and Other Opportunistic Infections, Including the Impact of HIV or SARS-CoV-2 in Adults
- **P.** Maternal and Fetal HIV or SARS-CoV-2: Transmission, Prevention, Treatment, Pregnancy, and Postpartum Maternal Health
- **Q.** HIV, SARS-CoV-2, or Both in Infants, Children, and Adolescents

### Epidemiology/Public Health

- **R.** Epidemiology of HIV and COVID-19 in Adults
- **S.** Epidemiology of COVID-19
- **T.** HIV Testing in Adults: New Diagnostics, Population Studies, and Scale-Up
- **U.** COVID-19 Testing: New Diagnostics for Virus, Viral Variants, and Antibodies; Testing in Various Populations; and Scale-Up
- **V.** HIV Prevention Interventions in Adults
- **W.** COVID-19 Prevention Interventions in Adults

### Prevention and Treatment

- **X.** Contraception, Sexually Transmitted Infections, and Reproductive Health in Adults
- **Y.** Implementation and Scale-Up of Prevention and Treatment for HIV and Impact of COVID-19 on HIV-Related Programs

For more information, visit the CROI Abstract Categories webpage. Note, abstracts that were submitted in categories designated with the letters C, S, U, and W were integrated into other categories.

## Abstract Content

Author names, institutions, titles, and abstracts in the CROI Program Guide, Abstract eBook, Conference Platform, and other materials are presented largely as provided 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 complete and accurate contact information for all authors, including email addresses.

## Special Notes on Abstract Content

Presentations from randomized trials and cohorts should follow the 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 epidemiological studies, the presentation should provide sex-stratified results or identify who was included if it includes only a single population. Appropriate terminology such as "cisgender" (people whose gender matches 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 the 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.

For abstracts that include serologic tests for SARS-CoV-2, the type of serologic test should be described.

For abstracts describing new compounds, the chemical or molecular structure must be shown in the presentation (it need not be part of the abstract or be published in the abstract eBook).

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

Please also note whether the study is ongoing or completed and whether the results are preliminary or final.

## Presenter Responsibilities

Visit the Invited Presenter, Oral Abstract Presenter, and Poster Presenter webpages for information regarding presenter responsibilities.

## Abstract Review Process

For information, visit the Abstract Guidelines and Submission webpage.

## Embargo and Press Release Policies

For information, visit the Embargo and Press Release Policies webpage.

## Statistics for Abstracts

General Abstracts Submitted ..... 1508
General Abstracts Accepted ..... 860
  General Oral Abstracts Accepted ..... 92
  General Poster Abstracts Accepted ..... 768
Late-Breaking Abstracts Submitted ..... 72
Late-Breaking Abstracts Accepted ..... 38
  Late-Breaking Oral Abstracts .....17
  Late-Breaking Poster Abstracts ..... 21
**Total Abstracts Submitted** .....1580
**Total Abstracts Accepted** ..... 898

## Abstracts Related to SARS-CoV-2 or Special Study Populations

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Adolescents ..... 48
Men Who Have Sex With Men (MSM) ..... 94
People Who Inject Drugs (PWID) ..... 39
Transgender Men or Women ..... 37
Women ..... 130

Authors have noted specific populations as the focus of their study, if applicable.

# ORAL ABSTRACTS



## 1 SCOTT M. HAMMER WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES

**Serena S. Spudich**[1]
[1]*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, the presentations will cover HIV and SARS-CoV-2. The program will begin with a presentation by Dr Theodora Hatziioannou on novel aspects of the HIV-1 and SARS-CoV-2 replication cycles, with an emphasis on the similarities and differences between the two viruses. Following this, Dr Penny Moore will cover the immune responses against HIV and SARS-CoV-2. Dr Carlos del Rio will outline the most efficient prevention measures for controlling the COVID-19 pandemic and will review therapeutic strategies and currently available SARS-CoV-2 vaccines. In the next presentation, Dr Adaora Adimora will address advances in different biomedic strategies for the prevention of HIV transmission. Finally, Dr Peter W. Hunt will review advances in preclinical and clinical approaches for functional or sterilizing HIV-1 cure. By the completion of the workshop, attendees will have achieved a head start toward maximizing the knowledge gained and research ideas arising from CROI 2022.

## 2 WE'RE STILL HERE: HIV, AGING, AND THE INVISIBLE GENERATION

**Marc Thompson**[1]
[1]*PrEPSter, London, UK*

In this presentation, I will be referencing my own lived experience as a man living and aging with HIV to explore some of the key challenges and issues PWHIV face as we grow older. I will talk about the similarities and differences in aging with HIV across the diverse communities affected by HIV across the globe; the impact of long-term diagnosis, treatment, and stigma; how community and clinical services are meeting the needs of an aging demographic. I will discuss models of good practice and how we can prepare for a population of PWHIV to enable them to live well as they age. I will also make a call to action for CROI attendees to improve, practice, and develop research that understands the emerging needs of people aging with HIV and actively involves patients and the community engages.

## 3 VACCINE STRATEGIES FOR HIV-1 AND COVID-19

**Dan Barouch**[1]
[1]*Beth Israel Deaconess Medical Center, Boston, MA, USA*

In this lecture, I will review the 40-year history of HIV-1 vaccine development and the 2-year history of COVID-19 vaccine development. Despite decades of scientific discoveries, the world still does not have a safe and effective HIV-1 vaccine. In contrast, multiple highly effective vaccines for COVID-19 were developed in record time. I will review key advances made in the HIV-1 research field that facilitated the development of COVID-19 vaccines. I will also discuss the epidemiology and virology of these two contrasting pandemics and the current state of knowledge of immunologic correlates of protection, and I will provide perspectives on future directions for the HIV-1 and COVID-19 vaccine fields.

## 4 HIV PREVENTION IN VULNERABLE POPULATIONS: GENERATING EVIDENCE TO REDUCE INEQUALITIES

**Beatriz Grinsztejn**[1]
[1]*Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil*

The HIV epidemic in Latin America remains concentrated in large urban centers, with vulnerable populations suffering the highest burden, particularly MSM and transgender women. In the last 10 years, the number of new HIV infections remained high and stable, and although ART coverage led to a significant decrease in AIDS-related mortality, the decrease was lower in Latin America when compared to the other regions. Brazil accounts for more than one-third of the HIV burden of the region. It was the first low-/middle-income country to provide access to universal treatment to individuals living with HIV. Brazil's actions towards the AIDS crisis assumed a human rights-based approach, integrating both prevention and treatment efforts into its universal health care system. Brazil's civil society organizations play a crucial role in shaping the initial and ongoing response. Since 2014, a "Treat All" policy of providing antiretroviral treatment in addition to comprehensive services including HIV testing and laboratory monitoring, and pre-exposure prophylaxis has been in place. The impact of the policies on people living with HIV resulted in an improved quality of life and a decline in overall morbidity and mortality. Nonetheless, important challenges remain, including a high and stable HIV incidence among key populations, and a high prevalence of late treatment initiation and of early mortality from AIDS causes, impacting the multiple steps of the continuum of care. This presentation will (a) present recent epidemiologic data on the HIV epidemic in Latin America, (b) describe and detail the characteristics of the Brazilian response to the HIV epidemic and the current status of the epidemic in Brazil, and (c) share Brazil's contribution to cutting edge AIDS research and its impact on public health policies. The latter will focus on how the data emanating from research efforts have contributed to major innovations for the HIV prevention and care agenda. Areas highlighted include pMTCT, tuberculosis, ART strategies for treatment and prevention including pre-exposure prophylaxis, and vulnerable populations, particularly young MSM and transgender women, HPV, reproductive health, and COVID-19. These research advances were only made possible through close engagement with the community. It is through this strong community engagement that we aim to reduce stigma and discrimination while promoting human rights.

## 5 POPULATION LEVEL VIRAL SEQUENCING

**Tulio De Oliveira**[1]
[1]*University of KwaZulu-Natal, Durban, South Africa*

The COVID-19 pandemic is one of the greatest challenges that humankind has faced in generations. It has already cost more than five million lives globally, sickened over 300 million people around the world, upended countless livelihoods, and caused substantial economic loss. Despite advances in the development and rollout of vaccines as well as in the clinical management of patients with COVID-19, the end of the worst public-health crisis in a century is not yet in sight as new variants that decrease the effectiveness of the public health interventions and vaccines continue to emerge. Since the beginning of the pandemic, there have been multiple SARS-CoV-2 variants across the world. The early COVID-19 pandemic was dominated by the D614G mutation, which was more transmissible. Over the past two years, several more variants have been identified with five becoming rapidly dominant within their countries and have raised concerns, including: Alpha (B.1.1.7 / VOC-202012/01), Beta (501Y.V2 / B.1.351), Gamma (P.1 / B.1.1.28.1), Delta (B.1.617.2) and Omicron (B.1.1.529). This presentation reflects on the identification, through genomic surveillance, and public health response to variants of concern in South Africa with a particular focus on the Beta and Omicron variants that were first identified in the country. South Africa has experienced four distinct waves. The first was associated with a mix of SARS-CoV-2 lineages, while the second and third waves were driven by

the Beta and Delta variants, respectively. The most recent wave was dominated by the Omicron variant. In November 2021, genomic surveillance teams in South Africa and Botswana detected a new SARS-CoV-2 variant associated with a rapid resurgence of infections in Gauteng Province, South Africa. Within three days of the first genome being uploaded, it was designated a variant of concern (Omicron) by the World Health Organization and, within three weeks, had been identified in 87 countries. The Omicron variant is exceptional for carrying over 30 mutations in the spike glycoprotein, predicted to influence antibody neutralization and spike function. The genomic profile, early transmission, and rapid spread of Omicron will be highlighted.

**6 DEEP MUTATIONAL SCANNING TO INTERPRET VIRAL EVOLUTION**

**Jesse D. Bloom**[1]
[1]*Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

Advances in genome sequence have enabled rapid identification of new SARS-CoV-2 variant lineages, but a major challenge is understanding how mutations in these variants will affect anti-viral immunity. Here I describe new high-throughout assays that provide data that can be used to rapidly interpret the consequences of SARS-CoV-2 mutations.

**7 AI-INSPIRED MONOCLONAL THERAPEUTIC ANTIBODY DESIGN**

**Regina Barzilay**[1]
[1]*Massachusetts Institute of Technology, Cambridge, MA, USA*

Artificial intelligence (AI)-inspired monoclonal therapeutic antibody designs are a recent development that have enabled new treatment methods. In this presentation, Dr Barzilay will discuss the power of AI and machine learning (ML) in developing drugs. She will also review potential approaches to applying AI and ML to understanding antibody activity and to designing novel monoclonal drugs in the prevention and treatment of HIV.

**8 SINGLE-CELL PROTEOMICS**

**Nikolai Slavov**[1]
[1]*Northeastern University, Boston, MA, USA*

Recently, the throughput of single-cell RNA-sequencing (transcriptomics) and genomics technologies has increased more than a 1000-fold. This increase has powered new analyses: Whereas traditional analysis of bulk tissue averages all differences between the diverse cells comprising such samples, single-cell analysis characterizes each individual cell and thus has enabled the discovery and classification of previously unknown cell states. Yet, the nucleic-acid–based technologies are effectively blind to an important group of biologic regulators: proteins. Fortunately, emerging mass-spectrometry (MS) technologies that identify and quantify proteins promise to deliver similar gains to single-cell protein analysis. These proteomic technologies will enable high-throughput investigation of key biologic questions, such as signaling mechanisms based on protein binding, modifications, and degradation, that have long remained elusive. I will discuss examples of applying single-cell proteomics to characterizing cell heterogeneity and regulatory mechanisms in immune systems and future prospects for advancing single-cell proteomics technologies and expanding the scope and scale of their applications.

**9 LIVER STEATOSIS IN PERSONS LIVING WITH HIV**

**Maud Lemoine**[1]
[1]*Imperial College London, London, UK*

Liver steatosis is a frequent finding in people living with HIV (PLWH). In the absence of excessive alcohol intake or coinfection with viral hepatitis, metabolic syndrome is the main cause of hepatic steatosis, known as non-alcoholic fatty liver disease (NAFLD). Due to the growing burden of metabolic syndrome in PLWH, NAFLD has become a common cause of chronic liver disease in this population, with an estimated prevalence of 35% in HIV-monoinfected individuals. NAFLD encompasses a spectrum of diseases from simple liver steatosis, to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis and its complications. Although data on NAFLD in PLWH is heterogeneous and its clinical impact needs to be better documented, it is now well established that metabolic factors, especially high body mass index (BMI) and type 2 diabetes, are key factors associated with liver steatosis, fibrosis, and cirrhosis in this patient group. The independent role of HIV infection and antiretroviral therapy (ART) is less well defined in NAFLD. In a new era where body weight of PLWH is growing due to aging, sedentarism, and exposure to new ART, the diagnosis of NAFLD is important. Despite some controversy in this population, non-invasive markers (eg, CAP-Fibroscan, FIB-4) are recommended to identify patients with liver steatosis and advanced fibrosis. Liver biopsy should still be considered to confirm the diagnosis of NASH or suspected advanced liver fibrosis. In the absence of licensed therapy specific for NAFLD, the control of metabolic syndrome combined with lifestyle changes should be initiated in all PLWH with NAFLD. Finally, the inclusion of PLWH in NAFLD clinic trials should be urgently considered.

**10 GETTING HEPATITIS C AGAIN**

**Maria Prins**[1]
[1]*Academic Medical Center, Amsterdam, Netherlands*

Sharp declines in the incidence of hepatitis C virus (HCV) have coincided with unrestricted access to direct-acting antivirals (DAA) against HCV, particularly among PLHIV in clinical care. However, rates of HCV reinfection are still high among specific key populations at risk of or living with HIV. This presentation begins with a case highlighting one individual's experience with PrEP use and HCV re-infection. An overview is then provided of the most recent data on the risk of HCV primary and re-infection among key populations, focusing on MSM and PWID. The potential effect of COVID-19 restrictions on HCV infection rates is also addressed. Issues regarding the role of testing, early diagnosis, and treatment in the acute phase of HCV infection, as well as the implications surrounding chemsex, are explored and recommendations for a comprehensive strategy to prevent new HCV infections are provided.

**11 CONTROVERSIES IN HEPATITIS B**

**Chloe L. Thio**[1]
[1]*The Johns Hopkins University, Baltimore, MD, USA*

This presentation will focus on three controversies in hepatitis B treatment in people living with and without HIV infection. Controversies discussed include discontinuing nucleoside analogue therapy, screening for HCC with long-term suppression of HBV DNA on nucelos(t)ide analogue therapy, and treatment of immunotolerant chronic hepatitis B. The most recent data on these controversies will be reviewed.

**12 THE ORIGINAL DELTA VIRUS OR D LIKE THE DEVIL**

**Markus Cornberg**[1]
[1]*Medizinische Hochschule Hannover, Hannover, Germany*

Hepatitis D or delta virus (HDV) is an "original" RNA virus that requires the hepatitis B surface antigen (HBsAg) of hepatitis B virus (HBV) for transmission. The worldwide prevalence of HDV infection is difficult to classify. Recently, several systematic reviews have been published on this topic, reporting a worldwide prevalence of between 12 and 70 million. The high range documents the uncertainty and insufficient data quality. One reason for the unclear epidemiologic data is that anti-HDV screening is not regularly performed in patients who are HBsAg-positive. Even in the international guidelines, there are different recommendations on who should be screened for hepatitis D. Although the EASL CPG recommends HDV screening in all HBsAg positive patients, the AASLD guidelines recommend it only in patients with a risk profile. Chronic HDV infection is associated with a severe course of hepatitis, often leading to rapid progression of fibrosis, hepatic decompensation, and HCC. Therefore, effective therapeutic options are crucial. Until recently, only PEG-IFN was available as a therapeutic option with 25% to 30% of patients achieving virologic response. However, therapy with PEG-IFN cannot be used in many patients with hepatitis D because of contraindications. New therapeutic options are already being tested in phase III trials. Very recently, EMA approved the HDV entry inhibitor bulevirtide at a dose of 2 mg SC once daily as a therapy for hepatitis D in compensated liver disease. Bulevirtide is a lipopeptide that blocks the function of the HBV receptor NTCP. The basis for this approval is the results of 2 phase II trials that tested bulevirtide in patients with chronic hepatitis D. The primary endpoint of the study, an undetectable HDV RNA concentration or a reduction of 2log10 copies or greater from study entry to week 24, was achieved in approximately 50% of patients and ALT normalized in more than 40%. The therapy was very well tolerated according to the congress reports and also from my own experience. After cessation of therapy, virologic relapse occurs in most patients, so the optimal duration of treatment has not yet been defined. Bulevirtide is also being investigated in combination with PEG-IFN and other drugs with different mechanisms of action (eg, the prenylation inhibitor lonafarnib) are clinical development. Thus, there are important developments in the treatment of this most severe form of chronic viral hepatitis.

**13 STUDYING COVID TREATMENT OUTCOMES: WHY DISPARATE RESULTS?**

**Eric J. Rubin**[1]
[1]*New England Journal of Medicine, Boston, MA, USA*

Research during the COVID-19 outbreak has followed a pattern: observational data and case series followed by more rigorous randomized-controlled trials. The results of these trials have sometimes been inconsistent. Disparate results have arisen from small sample sizes, small changes in protocols, and relatively small effect sizes. These issues can affect any clinical trial but the differences are magnified by the number of simultaneous studies asking very similar questions and the incredible attention that has been paid to results. Here I will discuss the sources of discrepancies and their importance and how some of these issues could be resolved in the future.

**14 ANALYSIS APPROACHES TO CORRELATES OF VACCINE EFFICACY**

**Peter Gilbert**[1]
[1]*Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

Vaccines are approved by regulatory agencies based on randomized, placebo-controlled vaccine efficacy (VE) trials that demonstrate vaccination is safe and reduces the risk of acquisition of an infectious disease clinical endpoint. The resource intensity of VE trials makes it difficult to base vaccine approval on this gold-standard approach for every indication of interest (defined by host population, virus strain population, and/or the specific vaccine regimen). Therefore, an important objective in vaccinology is to develop 'immune marker surrogate endpoints' that can be used as primary endpoints in smaller and faster studies for provisional or traditional approval of vaccines. After summarizing why immune correlates are needed, the talk summarizes approaches to the evaluation of the quality of an immune marker as a surrogate endpoint for a clinical endpoint based on VE trials and on other evidence sources (lab development of immunoassays/biomarkers, natural history studies, post-approval epidemiological studies, vaccine mechanism studies, meta-analysis of multiple VE trials). In VE trials, data analysis evaluates 'correlates of risk' (CoRs) and 'correlates of protection' (CoPs) as distinct objectives. CoR analysis assesses the association of an immune marker with the acquisition of the clinical endpoint in vaccine recipients. CoR analysis estimates association parameters and is limited in that it does not assess a causal effect of vaccination, such that an immune marker may be a CoR but fail to be a CoP. CoP analysis, on the other hand, studies how immune markers predict, cause, or mediate VE, with goal to generate evidence of whether and how an immune marker can be used to reliably predict VE against the clinical endpoint. An immune marker with established robust evidence for providing this reliable prediction can be designated a 'non-validated surrogate endpoint' or 'validated surrogate endpoint' (depending on evidence level) and thus be used for provisional or traditional vaccine approval, respectively. The talk summarizes statistical approaches for evaluating CoRs and CoPs in VE trials, illustrated by the Moderna COVID-19 VE trial. Approaches to evaluating CoPs include controlled direct effect analysis that assesses the causal effect of the marker on reducing risk and mediation analysis that assesses how much of the vaccine's overall efficacy is mediated through the marker. Meta-analysis quantifies how well VE can be predicted by an immune marker.

**15 ASSESSING VACCINE EFFECTIVENESS IN THE REAL WORLD**

**Sheena G. Sullivan**[1]
[1]*University of Melbourne, Melbourne, Australia*

The test-negative design has been used to estimate influenza vaccine effectiveness (VE) for many years and has more recently been employed for the estimation of COVID-19 VE. In these studies, patients meeting a pre-specified clinical case definition are tested for the disease of interest. Vaccine coverage is compared between those testing positive versus those testing negative to estimate VE. The key advantage of the test-negative design is cost-it can easily be incorporated into surveillance systems or applied to health management data if diagnostic and vaccination records are available. The design has been extensively validated for influenza but its adoption for COVID-19 has not always been accompanied by an assessment of its suitability to the data available. Blind application of the design may not overcome serious validity issues, especially when using administrative data. First, the test negative design reduces selection bias associated with differential health care-seeking behavior by vaccination status when patients are recruited based on clinical criteria thereby confirming they would have presented for testing when ill irrespective of vaccination. In studies where patients are tested for reasons other than symptoms, vaccine coverage in the test-negatives may not be representative of the source population. Second, the test-negative design should reduce outcome misclassification, because all participants are tested for the disease of interest. However, in the context of low prevalence or the use of less sensitive and less specific rapid antigen tests, the probability of misclassifying a case may increase. Third, test negative studies may be vulnerable to exposure misclassification, particularly when vaccination records must be linked to testing or case management records. Finally, test-negative studies cannot overcome the bias associated with confounding if relevant variables are unmeasured. For example, in a tiered vaccination framework, which prioritizes high-risk groups, information about vaccination eligibility is required for appropriate adjustment. The extent to which these biases might distort VE estimates will be explored using causal graphs and simulations. Rapid dissemination of COVID-19 VE estimates has been vital for ongoing pandemic management, but the speed with which estimates can be made should not come at the expense of validity.

**16 HIV NONHUMAN PRIMATE MODELS FOR STUDIES OF VIRUS PATHOGENESIS, PERSISTENCE, AND CURE**

**Michaela Müller-Trutwin**[1]
[1]*Institut Pasteur, Paris, France*

More than 40 years after the first report of AIDS, and despite tremendous progress in treatment and prevention against HIV infection, no vaccine or cure is available. There is a strong need for a better understanding of host immune responses and viral reservoirs in tissues. Recent results in HIV cure research indicate that a combination of strategies might be necessary to achieve durable remission or eradication of HIV. However, the number of combinations that can be tested is limited and need optimal guidance. Animal models allow deeper insights into tissue host-virus interactions and to perform mechanistic as well as proof-of-concept studies. The main NHP models correspond to macaques, where SIVmac infection displays similar replication profiles as HIV in humans, or macaques infected by a recombinant virus (SHIV) expressing HIV-1 ENV for analyzing the efficacy of bnAbs. Lessons for viral reservoir control and tissue damage protection can also be obtained from studying the natural host of SIV (African green monkeys, sooty mangabeys). Of note, no animal model is perfect. Examples of pitfalls will be discussed, as well as limitations of NHP models with regard to human studies. NHP models allowed nonetheless to significantly increase our understanding of HIV pathogenesis in fundamental aspects. In addition, studies with NHP models also gave important insights into mechanisms of viral reservoir establishment and control, contributing to HIV cure research. NHP models also sometimes revealed informative for the development of novel explorative approaches toward HIV cure. Recently, the role of innate immunity, in particular the role of NK cells, for viral reservoir control within tissues has gained increased interest. NK cells have been known for long for being able to eliminate abnormal and/or infected cells, through distinct mechanisms, including ADCC. Studies of macaques and AGM chronically infected by SIV have revealed the presence of adaptive and memory NK cells. The differentiation into potent NK cells might be tissue environment specific. Cytokine-induced, MHC-E dependent SIV-Env specific adapted and highly differentiated NK cells have been shown to be associated with reduction of replication-competent virus in lymph nodes from SIV-infected macaques under ART and with a delay of viral rebound after treatment interruption. Insights on tissue-specific immune responses and NK cells in NHP models with regard to their impact for HIV cure research will be discussed.

**17 CHILDREN EXPOSED TO HIV, BUT UNINFECTED: EVIDENCE FOR ACTION**

**Andrew J. Prendergast**[1]
[1]*Queen Mary University of London, London, UK*

Due to the success in preventing vertical transmission of HIV, there is an expanding global population of children who are HIV-exposed but uninfected (CHEU). Prior to the availability of antiretroviral therapy (ART) for pregnant and breastfeeding women, CHEU had evidence of excess mortality, morbidity, and growth failure compared to children who are HIV-unexposed (CHU), particularly in sub-Saharan Africa. Following the expansion of ART to prevent vertical transmission of HIV, it is becoming apparent that there are persistent health disparities between CHEU and CHU in the current era. This talk will focus on the current global population of children who are HIV-exposed but uninfected; the evidence for impaired health, growth, and development in CHEU; the

potential underlying mechanisms; and plausible interventions to reduce health disparities.

## 18 HIV INFECTION OF BRAIN ORGANOID MICROGLIA INDUCES INFLAMMATION AND NEURONAL DEATH

New Investigator Scholar

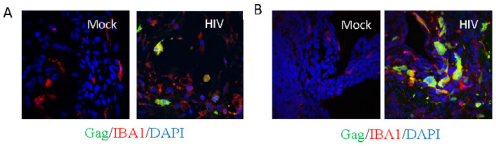
**Weili Kong**[1], Gang Zhang[1], Peter Sohn[1], Roland Schwarzer[1], Guorui Xie[1], Julie Frouard[1], Mauricio Montano[1], Nadia Roan[1], Li Gan[1], Warner Greene[1]
[1]*Gladstone Institutes, San Francisco, CA, USA*

**Background:** Although antiretroviral therapy (ART) has revolutionized clinical management and outcomes in HIV-infected individuals, HIV-associated neurocognitive disorder (HAND) remains prevalent. Microglia constitutes primary cellular targets for HIV in the brain, yet how infection of these cells culminates in the neuronal dysfunction and death observed in HAND remains poorly understood.

**Methods:** We established and tested two iPSC-derived brain organoid models: cerebral organoids and choroid plexus (ChP) organoids. ELISA, RT-PCR, and immunostaining were used to confirm HIV infection and to analyze the production of chemokines and cytokines. Single-cell RNA seq (scRNA-seq) was used to analyze how HIV infection alters microglial gene expression. RT-PCR and immunostaining were employed to validate the scRNA-seq findings.

**Results:** Following HIV infection in both brain organoid models, microglia was identified as the most prominently infected cell type. Infection was associated with marked gene expression induction of the chemokines CCL2 and CXCL10. These chemokines promote recruitment of T cells and monocytes to cross the blood-brain barrier contributing to development of HAND. Although ART efficiently inhibited HIV replication in the ChP organoids, low-level production of these inflammatory chemokines persisted despite ART. scRNA-seq studies indicated that HIV-infected microglia present within ChP organoids launches an inflammatory response that extends to mature and immature ChP cells and surrounding stromal cells. This inflammatory response correlated with activation of several members of the S100 family of genes (S100B, S100A8, and S100A9) that regulate diverse cellular processes including inflammation, proliferation, migration, apoptosis, energy metabolism, and others. The S100 protein family has been implicated in several neurologic disorders including HAND. Importantly, HIV infection in microglia also promoted inflammatory responses in bystander neurons leading to decreased mitochondrial energy generation, diminished neurotransmitter transport, and increased neuronal cell death.

**Conclusion:** HIV infection of microglia activates a circuit of genes including specific chemokines promoting immune cell migration into the brain and members of S100 gene family that further stimulate the inflammatory response. In this inflammatory environment, neurons become progressively dysfunctional and ultimately die by apoptosis. These events likely play a key role in the progressive development of HAND.




**A.** Cerebral organoids were either mock-treated or exposed to HIV-1 ADA at day 14 and analyzed on day 54. **B.** ChP organoids were either mock-treated or exposed to HIV-1 ADA at day 14 and analyzed on day 50. Immunofluorescence staining shows HIV-1 (anti-Gag, in green) and microglia (anti-IBA1, in red), together with DAPI DNA staining (in blue). Magnification is 60X for all panels.

## 19 MACROPHAGES ARE THE PRIMARY SOURCE OF VIRUS IN SEMEN IN ACUTELY INFECTED MACAQUES

**Christine M. Fennessey**[1], Catherine Brands[1], Simona Florea[1], Laura Newman[1], Leslie Lipkey[1], William Bosche[1], Randy Fast[1], Jeffrey D. Lifson[1], Brandon Keele[1], Claire Deleage[1]
[1]*Frederick National Laboratory for Cancer Research, Frederick, MD, USA*

**Background:** Most new HIV infections result from sexual interactions with infected but untreated individuals. Semen is the main vector for viral transmission globally, however, little is known regarding the anatomic origin and form of virus in semen.

**Methods:** In this study, we were able to combine numerous new technologies to assess the origin of the virus present in the semen during acute SIV infection. Six rhesus macaques were challenged intravenously with SIVmac239M, a barcoded virus that allows for genetic tracking of individual viral lineages. Semen and blood samples were collected longitudinally for 17 days post-infection with all male genital tract (MGT) and multiple lymphoid tissues collected at necropsy and subjected to quantitative PCR, next generation sequencing of the viral barcode, and tissue analysis including RNAscope, DNAscope and immunophenotyping. Additionally, anti-CD45-alex594 was administrated prior to final semen collection at necropsy to track potential circulating leucocytes present in ejaculate.

**Results:** Extremely high levels of viral RNA (vRNA) were detected in seminal plasma (up to 10^9cp/ml) as well as comparable levels of cell associated vRNA and vDNA in seminal cells with detection starting as early as 4 days post-infection. RNAscope and immunophenotyping of seminal cells and MGT tissues revealed myeloid cells as the main source of virus (Fig.1), while CD4+T cells were harboring vRNA in lymphoid tissues. Importantly, these infected cells were not labeled with the fluorescent anti-CD45 Ab suggesting tissular origin of the infected cells at the time of ejaculation. Barcode sequences show evidence of an early compartment between seminal and blood plasma.

**Conclusion:** This study demonstrates the feasibility of tracking the anatomic origins of seminal virus in SIV infection and could provide novel characterization of the virus that drives sexual transmission globally. Extraordinarily high seminal VLs and massive numbers of infected cells might be associated with primary infection and if this occurs in humans, could help explain the high rate of transmissibility during primary infection.

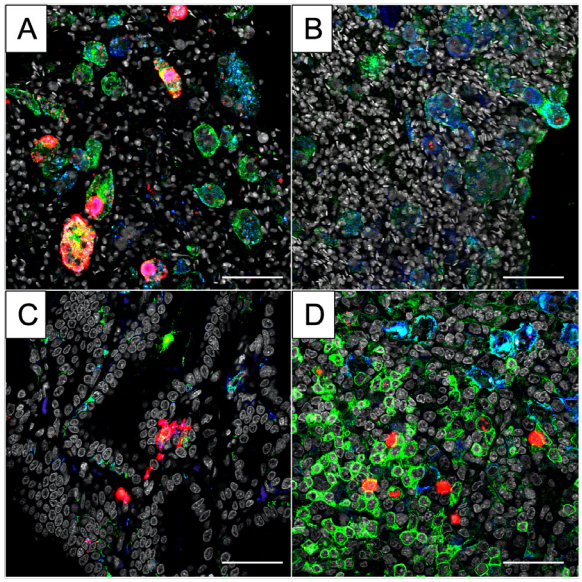



**Figure 1: Representative images of infected cells within the semen, MGT organs and lymph node.** In all panels, vRNA or vDNA is in red, CD4 in green, and CD206+CD68+CD163+ is blue. In seminal cell pellet, macrophages were found to harbor vRNA (A) and vDNA (B) to extremely high levels reflecting active replication. Macrophages vRNA positives were found within the lamina propria of seminal vesicle (C) but only CD4+T cells were found harboring vRNA within the lymph nodes (D). scale bars 100um.

## 20 CyTOF-Lec REVEALS GLYCAN FEATURES DEFINING CELLS DIFFERENTIALLY SUSCEPTIBLE TO HIV

New Investigator Scholar

**Tongcui Ma**[1], Matthew McGregor[1], Leila B. Giron[2], Mohamed Abdel-Mohsen[2], Nadia Roan[1]
[1]*Gladstone Institute of Virology and Immunology, San Francisco, CA, USA,* [2]*The Wistar Institute, Philadelphia, PA, USA*

**Background:** High-parameter single-cell phenotyping has enabled in-depth classification and interrogation of immune cells, but to date has not allowed for cell-surface glycan characterization.

**Methods:** To simultaneously characterize glycans + proteins at the single-cell level, we modified our recently established CyTOF panels. The resulting CyTOF-Lec panel was developed by conjugating lectins (glycan-binding proteins with known specificity) to metal lanthanides and combining these reagents with lanthanide-conjugated antibodies detecting protein antigens. By implementing CyTOF-Lec, we compared glycan features between different immune subsets from blood and tissue compartments (tonsils and genital biopsies)

before and after HIV infection. We then applied our recently established PP-SLIDE (predicted precursor single-cell linkage using distance estimation) bioinformatics approach to: 1) identify antigens differentially expressed on infected vs. uninfected CD4+ T cells; and 2) assess to what extent any differential expression was likely due to preferential infection of cellular subsets as opposed to up- or down-regulation of the antigen by HIV.
**Results:** We found that HIV upregulates the cell surface levels of fucose and sialic acid in a cell-intrinsic manner, and that memory CD4+ T cells co-expressing high levels of fucose and sialic acid are highly susceptible to HIV infection. Sialic acid levels were found to distinguish memory CD4+ T cell subsets expressing different amounts of HIV entry receptors (CD4, CCR5), pro-survival factors (OX40, Birc5), homing receptors (CCR7, CD62L), and activation markers (CD69, HLA-DR, and CD38). The CyTOF-Lec/PP-SLIDE results were validated in cell sorting experiments by demonstrating that HIV preferentially infected memory CD4+ T cells expressing high levels of sialic acid.
**CONCLUSION:** CyTOF-Lec and PP-SLIDE are promising tools for examining the cell-surface proteome + glycome of single cells. By applying these tools, we found that HIV remodels not only cellular proteins but also glycans, and that glycan expression can differentiate memory CD4+ T cells with vastly different susceptibility to HV infection. Given that very few markers have been identified that can distinguish, within memory CD4+ T cells, those that are differentially permissive to HIV, cell-surface glycans are promising markers of HIV-susceptible cells.

### 21 MONOMERIC HIV-1 ENVELOPE CYTOPLASMIC TAILS ARE SUFFICIENT FOR Gag LATTICE RETENTION

**Nicholas S. Groves**[1], Yuta Hikichi[2], Merissa Bruns[1], Eric O. Freed[2], Schuyler van Engelenburg[1]
*[1]University of Denver, Denver, CO, USA, [2]National Institutes of Health, Frederick, MD, USA*

**Background:** To combat the prevalence of Human Immunodeficiency Virus-1 (HIV-1) and emerging antiviral resistance, new antiviral classes must be pursued. An attractive target for new classes includes the virus assembly process. To create an infectious particle, the structural Gag polypeptide coalesces into a lattice on the plasma membrane of an infected cell. Coincidently, viral envelope glycoproteins (Env) must encounter and incorporate into an assembling Gag lattice. Released particles unable to obtain Env are non-infectious and unable to propagate HIV-1 infection. A requisite to the development of antivirals targeting Gag-Env coalescence is the need to define the functional units constituting this molecular interface.
**Methods:** HIV-1 envelope glycoproteins (Env) are well characterized to function as trimers for membrane fusion and entry, however, it is unclear whether the trimeric structure of Env is required for incorporation into virus particles. Using live-cell superresolution imaging and correlative single-particle tracking, we sought to determine the capabilities of Gag-MA to retain monomeric Env-CT. We also employed a competitive inhibition assay to understand whether the monomeric Env-CT could compete with WT Env trimers for the same sites of incorporation in the viral lattice.
**Results:** We determined that a monomeric receptor chimera containing the Env cytoplasmic tail, known to regulate Env incorporation, is sufficient for trimer-like retention in the Gag lattice. By co-expressing the synthetic Env-CT monomers and WT Env in producer cells, we also demonstrate that native Env incorporation can be potently restricted.
**Conclusion:** Our results suggest a mechanism in which Env must compete for a limited number of interaction sites in each assembling particle, and that these sites are not uniquely evolved to accommodate a trimeric Env-CT tail structure. Further, we demonstrate that Env-CT monomers can restrict incorporation of envelope glycoproteins from an evolutionarily distant HIV-1 primary isolate. Our findings support a model where a single Env-CT mediates Env incorporation, with this mechanism of envelope glycoprotein incorporation being conserved between distant clades of HIV-1.

### 22 RAPALOGS DOWNMODULATE INTRINSIC IMMUNITY AND PROMOTE CELL ENTRY OF SARS-CoV-2

**Guoli Shi**[1], Abhilash I. Chiramel[2], Saliha Majdoul[1], Kin Kui Lai[1], Swagata Kar[3], Sonja M. Best[2], Alex A. Compton[1]
*[1]National Cancer Institute, Frederick, MD, USA, [2]National Institute of Allergy and Infectious Diseases, Hamilton, MT, USA, [3]BIOQUAL, Inc, Rockville, MD, USA*

**Background:** SARS-CoV-2 infection in immunocompromised individuals has been associated with prolonged virus shedding and the development of novel viral variants. Rapamycin and rapamycin analogs (rapalogs, including everolimus, temsirolimus, and ridaforolimus) are FDA-approved for use as mTOR inhibitors in multiple clinical settings, including cancer and autoimmunity, but a common side effect of these drugs is immunosuppression and increased susceptibility to infection. Immune impairment caused by rapalog use is traditionally attributed to their impacts on T cell signaling and cytokine production.
**Methods:** We used replication-competent SARS-CoV-2 and HIV pseudotyped with betacoronavirus Spike proteins to assess how rapalog pretreatment of cells ex vivo and rodent animals in vivo impacts susceptibility to Spike-mediated infection.
**Results:** We show that exposure to rapalogs increases cellular susceptibility to SARS-CoV-2 infection by antagonizing components of the constitutive and interferon-induced cell-intrinsic immune response. Pre-treatment of cells (including human lung epithelial cells and primary human small airway epithelial cells) with rapalogs promoted the early stages of SARS-CoV-2 infection by facilitating Spike-mediated virus entry. Rapalogs also boosted infection mediated by Spike from SARS-CoV and MERS-CoV in addition to hemagglutinin of influenza A virus and glycoprotein from vesicular stomatitis virus, suggesting that rapalogs downmodulate antiviral defenses that pose a common barrier to these viral fusion proteins. By identifying one rapalog (ridaforolimus) that lacks this function, we demonstrate that the extent to which rapalogs promote virus entry is linked to their capacity to trigger the lysosomal degradation of IFITM2 and IFITM3, intrinsic inhibitors of virus-cell membrane fusion. Mechanistically, rapalogs that promote virus entry inhibit the mTOR-mediated phosphorylation of TFEB, a transcription factor controlling lysosome biogenesis and lysosomal degradation pathways such as autophagy. In contrast, TFEB phosphorylation by mTOR was not inhibited by ridaforolimus. In the hamster model of SARS-CoV-2 infection, injection of rapamycin four hours prior to virus exposure resulted in elevated virus titers in lungs, accelerated weight loss, and decreased survival.
**Conclusion:** Our findings indicate that preexisting use of certain rapalogs may elevate host susceptibility to SARS-CoV-2 infection and disease by activating a lysosome-mediated suppression of intrinsic immunity.

### 23 IFITM DEPENDENCY OF SARS-CoV-2 VARIANTS OF CONCERN

**Rayhane Nchioua**[1], Caterina Prelli Bozzo[1], Annika Schundner[2], Fabian Zech[1], Manfred Frick[2], Konstantin Sparrer[1], Frank Kirchhoff[1]
*[1]Ulm University Medical Center, Ulm, Germany, [2]Ulm University, Ulm, Germany*

**Background:** We recently showed that genuine SARS-CoV-2 hijacks endogenously expressed interferon-induced transmembrane proteins, especially IFITM2, as entry cofactors for efficient infection (Prelli Bozzo, Nchioua et al., Nat. Com., 2021). This came as a surprise, since IFITMs have been reported to inhibit entry of numerous enveloped viruses, including SARS-CoV-2. However, most data were obtained using IFITM overexpression and pseudoparticle infection assays. In our initial study, we used a SARS-CoV-2 strain isolated in the Netherlands in February 2020 (NL-02-2020). Since then several "variants of concern" (VOCs) have emerged that show increased transmission fitness and evasion of vaccine-induced immunity. These VOCs contain various alterations in their Spike (S) proteins that may alter their dependency on entry cofactors. Here, we examined whether SARS-CoV-2 VOCs, including the currently dominating Delta variant, still depend on IFITMs for efficient infection and replication.
**Methods:** To determine the role of IFITMs in infection of SARS-CoV-2 VOCs, we silenced IFITM1, 2, or 3 expression in Calu-3 cells using siRNAs and infected them with NL-02-2020 as well VOCs B.1.1.7, B.1.351, P.1 and B.1.617.2, also referred to as Alpha, Beta, Gamma and Delta variants, respectively. Viral entry and replication were quantified by qRT-PCR as well as TCID50 analysis. In addition, we determined the inhibitory effect of an α-IFITM2 antibody on VOC infection in iPSC-derived human alveolar epithelial type 2 (iAT2) cells.
**Results:** Depletion of IFITM2 reduced viral RNA production from 31- (B.1.1.7) to 754-fold (P.1). In comparison, KD of IFITM1 generally had little effect, while silencing of IFITM3 resulted in 2- to 20-fold reduction of viral RNA yields by the four VOCs. An antibody directed against the N-terminus of IFITM2 inhibited SARS-CoV-2 VOC replication in iAT2 cells.
**Conclusion:** Endogenously expressed IFITM proteins (especially IFITM2) are important cofactors for entry and replication of SARS-CoV-2 VOCs, including the Delta variant that currently dominates the COVID-19 pandemic.

## 24 INTERFERON RESISTANCE OF EMERGING SARS-CoV-2 VARIANTS

**Kejun Guo[1],** Bradley S. Barrett[1], Kaylee Mickens[1], Eszter Vladar[1], James Morrison[1], Kim J. Hasenkrug[2], Eric M. Poeschla[1], Mario L. Santiago[1]
*[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]National Institute of Allergy and Infectious Diseases, Hamilton, MT, USA*

**Background:** The continuing spread of SARS-CoV-2 provides opportunities for the virus to evolve. Compared to ancestral strains, the 4 major variants of concern (VOC) exhibit Spike mutations that improve entry and/or diminish antibody neutralization. However, mutations have arisen in other viral genes. Several of these genes may counteract innate immunity mediated by antiviral interferons (IFNs). IFNs show extensive diversity, but only IFNα2 and IFNβ are approved for clinical use. We showed previously that diverse IFNs exhibit variable activities against HIV-1 and trigger distinct transcriptomes.

**Methods:** To assess whether SARS-CoV-2 acquired human IFN resistance over time, isolates representing early lineages A, B, B.1, and VOC lineages B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma) and B.1.617.2 (delta) were tested for sensitivity to multiple IFNs in an alveolar type II epithelial cell (AT2) line, A549, overexpressing ACE2. Cells were pre-treated with IFNs for 18 h in triplicate, then infected to yield ~10^5 copies/reaction. Virus copy numbers were evaluated at 24 h by qPCR. We compared the sensitivity of 5 SARS-CoV-2 isolates to 12 IFNα subtypes, IFNβ, IFNω and 3 IFNλ subtypes at 2 pM, within the dynamic range of preliminary IFN inhibition curves. $IC_{50}$s for IFNβ and IFNλ1 were compared between lineage B and VOC isolates.

**Results:** Among the 17 IFNs tested, IFNβ, IFNα8, IFNω and IFNα5 most potently inhibited SARS-CoV-2 in A549-ACE2 cells. Inhibition curves with a delta variant isolate showed that IFNα2 and IFNλ1 had >10-fold and >1000-fold higher $IC_{50}$ than IFNβ, respectively. Interestingly, the antiviral activity patterns of diverse IFNα subtypes against SARS-CoV-2 and HIV-1 were different and did not significantly correlate. Compared to the ancestral lineage B, the alpha, beta, gamma and delta variants exhibited on average 5.2-fold (range: 1.9-8.2) and 6.7-fold (range: 1.3-21) fold higher $IC_{50}$s for IFNβ and IFNλ1, respectively. The alpha and delta isolates were also more resistant to IFNβ and IFNλ1 than a lineage B.1 isolate in another AT2 cell line, Calu-3.

**Conclusion:** Our findings suggest that diverse IFNs may have evolved to restrict distinct virus families. Emerging SARS-CoV-2 variants are more effective than earlier pandemic viruses at antagonizing antiviral IFN responses. These data have implications for deploying IFNs for early COVID-19 therapy and suggest that innate immunity may be a driving force for SARS-CoV-2 evolution.

## 25 TYPE-I INTERFERON MODULATION IN VIVO BLOCKS SARS-CoV-2 REPLICATION AND INFLAMMATION

New Investigator Scholar

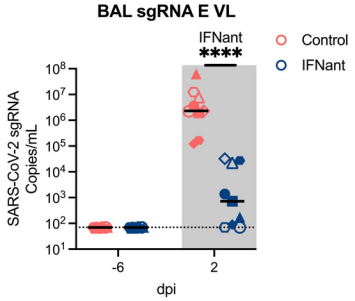
**Timothy Hoang**[1], Elise G. Viox[1], Amit Upadhyay[1], Maria Pino[1], Arun Boddapati[1], Gregory Tharp[1], Zachary Strongin[1], Thomas H. Vanderford[1], Monica Vaccari[2], Jacob Estes[3], Daniel C. Douek[4], Gideon Schreiber[5], Steven Bosinger[1], Mirko Paiardini[1]
*[1]Emory University, Atlanta, GA, USA, [2]Tulane National Primate Research Center, Covington, LA, USA, [3]Oregon Health and Sciences University, Portland, OR, USA, [4]National Institutes of Health, Bethesda, MD, USA, [5]Weizmann Institute of Science, Rehovat, Israel*

**Background:** Systemic and local inflammation following SARS-CoV-2 infection has been widely described and predictive of disease severity and death. However, the exact immune mediators driving inflammation contributing to SARS-CoV-2 host defense vs. those driving immune-mediated pathology in humans have not been fully elucidated. Deficiencies in type-I interferon (IFN-I) responses, including inborn errors to genes in the IFN-I pathway, neutralizing auto-antibodies against all subtypes of IFN-I, or the lack of production of IFN-I, are associated with severe COVID-19 in otherwise healthy individuals. Conversely, sustained IFN-I responses have been shown to contribute to severe COVID-19 by exacerbating inflammation, and prolonged IFN-I signaling has been shown to interfere with lung repair following viral infection and to increase susceptibility to bacterial infections. Thus, it is critical to understand the roles of IFN-I signaling in COVID-19 to design therapeutic strategies.

**Methods:** Here, we modulated IFN-I signaling in rhesus macaques (Macaca mulatta; RMs) from day -1 through day 2 post SARS-CoV-2 infection (dpi) using an IFN-I antagonist (IFNant). Eighteen RMs (9 control and 9 IFNant treated) were infected with SARS-CoV-2 on day 0, with 6 RMs sacrificed at 2, 4, and 7dpi. Nasal and throat swabs were collected for viral load; blood and bronchoalveolar lavage fluid (BAL) for flow cytometry and RNAseq.

**Results:** IFNant treatment prior to infection resulted in a highly significant and consistent reduction in SARS-CoV-2 viral load in the lower airways (>3-log difference; 2dpi BAL) and upper airways (nasal and throat swabs). Treatment with IFNant initiated also potently reduced: (i) soluble markers of inflammation in BAL, (ii) expansion of inflammatory monocytes (CD14+CD16+), and (iii) pathogenesis in the lung. Furthermore, Siglec-1 expression, which has been shown to enhance SARS-CoV-2 infection, was rapidly downregulated in the lung and in monocytes of IFNant-treated RMs. Remarkably, RNAseq analysis showed a robust reduction in pathways associated with inflammation and decreased levels of interferon-stimulated genes post-infection in treated RMs. Thus, IFNant treatment prior to infection resulted in limited viral replication, inflammation, and pathogenesis in SARS-CoV-2-infected RMs.

**Conclusion:** These data indicate a vital, early role of IFN-I in regulating COVID-19 progression and emphasize the importance of understanding IFN-I pathways in COVID-19 for the development of targeted therapeutic strategies.




## 26 SARS-CoV-2 SPIKE BINDS FIBRINOGEN-INDUCING ABNORMAL INFLAMMATORY BLOOD CLOTS

**Mauricio Montano**[1], Jae Kyu Ryu[1], Elif G. Sozmen[2], Karuna Dixit[1], Yusuke Matsui[1], Yixin Liu[1], Ekram Wassim A. Helmy[1], Thomas J. Deerinck[3], Zhaoqi Yan[1], Renaud Schuck[1], Reuben Thomas[1], Alexander R. Pico[1], Mark H. Ellisman[3], Katerina Akassaglou[1], Warner Greene[1]
*[1]Gladstone Institutes, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]University of California San Diego, La Jolla, CA, USA*

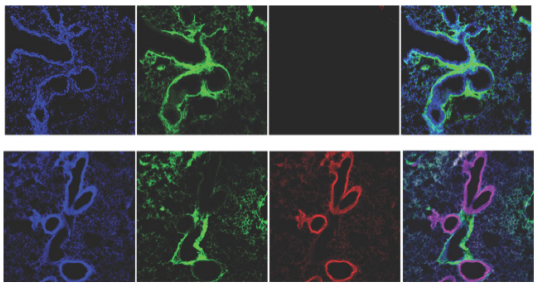
**Background:** Life threatening thrombotic events involving both the arterial and venous systems are prominently present in SARS-CoV-2 infected individuals presenting with severe COVID-19. Abnormal clotting also occurs in asymptomatically or mildly infected individuals and in people experiencing post-acute sequelae of SARS-CoV-2 infection (PASC). Clinical management of this clotting disorder has proven difficult in part because these fibrin clots are highly resistant to plasmin-mediated fibrinolysis.

**Methods:** An array of different binding, biochemical, microscopic, and in vivo assays were performed in these studies. All experiments were performed at least three times in triplicate and reported differences were shown to be statistically significant.

**Results:** We find that SARS-CoV-2 Spike directly binds to the terminal clotting factors, fibrinogen and fibrin (Kd of 5.3 μM and 0.4 μM respectively). Mixing Spike and plasma accelerates fibrin polymerization. Scanning electron microscopy reveals an abnormal clot structure with finer, denser, and roughened fibrin fibers. Scanning peptide competition assays indicate Spike binds fibrin at three sites: 1) the plasmin cleavage site needed for fibrinolysis; 2) a site involved in innate immune signaling via fibrin binding to Complement Receptor 3 (CR3); and 3) a site with no known function. Examination of mice injected 24h earlier with Spike pseudotyped HIV-ΔEnv virions reveals extensive intra- and extravascular fibrin deposition in the lung accompanied by endothelial activation, loss of tight junctions, increased influx of macrophages, and the generation of high levels of reactive oxygen species. This thromboinflammatory response is not observed when Bald virions are injected or when Spike pseudotyped virions are injected into mice lacking fibrinogen. Intriguingly, these Spike-induced proinflammatory effects are blocked by an anti-fibrin monoclonal antibody, 5B8, which interferes with fibrin binding to CR3.

**Conclusion:** Our findings reveal that the SARS-CoV-2 Spike protein binding to fibrinogen/fibrin results in the formation of structurally abnormal, fibrinolysis-resistant blood clots whose inflammatory effects are effectively neutralized by a specific fibrin-targeting monoclonal antibody. While COVID-19 clotting was thought to occur as a result of systemic inflammation, our findings suggest

clotting during SARS-CoV-2 infection in fact is a driver of inflammation. Targeting fibrin could lead to novel therapeutic approaches for patients with acute COVID-19 and PASC



Immunofluorescence staining of Claudin-1 tight junction protein and SARS-CoV-2 Spike in mouse lung tissue 24 hours after intravenous injection of Spike pseudotyped HIV virions or control BALD virions. Note loss of normal Claudin-1 staining in the presence of Spike indicating disruption of tight junction structure.

## 27 UNIVERSAL HEPATITIS C VIRUS SCREENING IN PREGNANCY: THE JUICE IS WORTH THE SQUEEZE

**Catherine A. Chappell**[1], Samantha M. Mayo[2], John A. Grosko[3], Leslie A. Meyn[2], Scott Henzler[3], Naudia Jonassaint[1], Sharon L. Hillier[1]
*[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Magee–Womens Research Institute, Pittsburgh, PA, USA, [3]University of Pittsburgh Medical Center, Pittsburgh, PA, USA*

**Background:** Recently, the American College of Obstetrics and Gynecology joined the CDC in recommending universal hepatitis C virus (HCV) screening of pregnant people. Universal HCV screening is hypothesized to increase the detection of HCV among pregnant people, resulting in fewer undetected perinatal HCV transmissions. Screening and case detection of HCV during risk-based vs. universal HCV screening among pregnant people attending care in Western Pennsylvania was compared.

**Methods:** Universal HCV screening was implemented in June 2020 using a Best Practice Alert in the electronic medical records (EMR) which provided a reminder if HCV testing was not ordered with the new OB panel and reflex testing for HCV RNA if IgG positive. HCV detection was compared using Fisher's exact test for all pregnant people presenting for prenatal care within one health system during two 12-month time periods: 1) risk-based HCV screening for 12,142 pregnant people (January 1-December 31, 2019) and 2) universal HCV screening for 12,588 pregnant people (July 1, 2020-June 30, 2021). The EMRs were reviewed for HCV testing nine months before and after initiation of prenatal care. Data from January to June 2020 was excluded due to concerns about poor health care utilization and disruptions in operations due to COVID-19.

**Results:** Universal HCV screening resulted in an increase in HCV IgG screening from 23% to 81% of people entering obstetrical care (p<0.001). The positivity rate of HCV IgG was higher among those who were tested using risk-based vs. universal screening (5.4% vs. 2.3%) (p<0.001). However, the prevalence of HCV IgG+ people was lower in the overall population using risk-based vs. universal screening (1.2% vs 1.9%) (p<0.001). Utilization of reflex HCV testing resulted in an increase in active HCV detected from 11 (0.091%) to 85 (0.68%) of the obstetrical population during the two 12-month monitoring periods (p<0.001). Given the HCV perinatal transmission rate of 5.8%, an additional 4 infants with perinatal HCV in 12 months were identified with universal screening that had previously gone undetected with risk-based screening within our system.

**Conclusion:** Risk-based HCV screening is insensitive for HCV detection within the general obstetric population. Our findings strongly support universal HCV screening of pregnant people not only to ensure that the pregnant person is linked to treatment, but also to ensure detection of all cases of perinatal HCV transmission.

**Table: Risk-Based Verses Universal Hepatitis C Virus Screening Among Pregnant People**

| | Risk-Based Screening (1/1/19-12/31/19) | Universal Screening (7/1/20-6/30/21) |
|---|---|---|
| Pregnant People | N=12,142 | N=12,588 |
| HCV IgG Tested | 2,749 (23%) | 10,167 (81%) |
| HCV IgG Positive | 148 (1.2%) | 237 (1.9%) |
| HCV RNA Tested | 33 (22% of HCV IgG+) | 225 (95% of HCV IgG+) |
| HCV RNA Positive | 11 (0.091%) | 85 (0.68%) |

## 28 HBIg-FREE STRATEGY TO PREVENT HBV MOTHER-TO-CHILD TRANSMISSION: ANRS TA PROHM STUDY

**Olivier Segeral**[1], Bunnet Dim[2], Christine Durier[3], Sovann Nhoeung[2], Kearena Chhim[4], Chantana Yay[5], Sothy Pech[6], Bunthoeun Nhem[7], Kay Huot[8], Chanlina Vong[9], Julia Guillebaud[2], Rattana Kim[6], Samsorphea Chhun[4], Laurence Borand[2]
*[1]University of Health Sciences, Phnom Penh, Cambodia, [2]Pasteur Institute in Cambodia, Phnom Penh, Cambodia, [3]Institut National de la Santé et de la Recherche Médicale, Villejuif, France, [4]Calmette Hospital, Phnom Penh, Cambodia, [5]Jayavarman VII- Kantha Bopha Hospital, Siem Reap, Cambodia, [6]National Maternal and Child Health Center, Phnom Penh, Cambodia, [7]Kampong Cham Provincial Hospital, Kampong Cham, Cambodia, [8]Takeo Referral Hospital, Takeo, Cambodia*

**Background:** In Cambodia, the prevalence of HBV infection among pregnant women, children aged 5 to 7 years, and those born to HBsAg-positive mothers was estimated at 4%, 0.6%, and 10%, respectively. While vaccination coverage is satisfactory, management of HBV infection during pregnancy is limited.

**Methods:** The objective was to evaluate the effectiveness of a strategy to prevent HBV MTCT based on: 1/the use of HBsAg/HBeAg RDTs algorithm to screen pregnant women and assess TDF eligibility 2/a TDF treatment from 24 weeks of amenorrhea for those eligible, 3/an early vaccination for all infants at birth (<2 hours of life). Positive HBsAg pregnant women were enrolled in a multicenter interventional prospective study. Women HBeAg-positive or HBeAg-negative & ALT≥40 IU/L in a second phase, received TDF from 24 weeks of amenorrhea to 6 weeks postpartum. Infants received hepatitis B birth-dose vaccine in delivery room (< 2 hours of life) then at 6, 10 and 14 weeks of age. HBIg were not recommended but could be done if accessible. The primary endpoint was the proportion of infants with plasmatic HBsAg positivity at 6 months of life, confirmed by HBV DNA detection.

**Results:** From October 2017 to December 2019, 21,251 pregnant women were screened for HBsAg, 1,339 were positive, 1,194 enrolled in the study and 338 TDF-eligible. At enrollment, median age was 29 years and median gestational age 23 weeks. The median HBV DNA level was 7.9 $\log_{10}$ IU/mL for TDF-eligible women and 2.5 $\log_{10}$ IU/mL for TDF-ineligible women. The proportion of eligible women starting TDF was 94% and 14.5% were treated less than 4 weeks prior delivery. The proportion of women with HBV DNA at delivery < 5.3 $\log_{10}$ IU/mL was 90% for those treated more than 4 weeks as compared to 50% for those treated less (p<0.001). At birth, 86% of infants received the first dose of vaccine ≤2 hours of life, 95% ≤24 hours of life and 15% received HBIg. Overall, HMB MTCT rate was 1.26% [0.34%-3.20%] and, in absence of HBIg, 1.48% [CI95%, 0.40-3.74] for TDF-eligible women: 0% [CI95%, 0-1.41] for those treated more than 4 weeks before delivery and 8.33% [CI95%, 1.75-22.5] for those treated less than 4 weeks. For TDF-ineligible women, the transmission rate was 0.98% [0.40-2.02] and 1.06% [CI95%, 0.39-2.30] in absence of HBIg.

**Conclusion:** An HBIg-free strategy was effective to prevent HBV MTCT if TDF was administrated for at least 4 weeks before delivery. This strategy could allow decentralization of HBV PMTCT to rural areas where most of pregnancies are managed.

Table 1: HBV transmission rate according to HBIg status and TDF duration

| | TDF-eligible | | | |
|---|---|---|---|---|
| **Variable** | **No** | | **Yes** | |
| | **n [N][1]** | **%[95%CI]** | **n [N][1]** | **%[95%CI]** |
| **Positive HBsAg whatever HBIg status** | | | | |
| Overall | 7 [712] | 0.98 [0.40-2.02] | 4 [317] | 1.26 [0.34-3.20] |
| According to TDF duration[2] | | | | |
| ≤ 4 weeks | | | 3 [46] | 6.52 [1.37-17.90] |
| >4 weeks | | | 0 [254] | 0 [0-1.44] |
| Never started treatment | | | 1 [10] | 10 [0.25-44.50] |
| **Positive HBsAg for infants without HBIg** | | | | |
| Overall | 6 [567] | 1.06 [0.39-2.30] | 4 [271] | 1.48 [0.40-3.74] |
| According to TDF duration | | | | |
| ≤ 4 weeks | | | 3 [36] | 8.33 [1.75-22.47] |
| >4 weeks | | | 0 [227] | 0 [0-1.61] |
| Never started treatment | | | 1 [8] | 12.5 [0.32-52.65] |

[1] n [N]: number of event, number of participants

[2] 0[7]: Missing data for date of delivery

## 29 THE IMPACT OF COVID-19 ON ADVERSE BIRTH OUTCOMES IN BOTSWANA BY HIV STATUS

New Investigator Scholar

**Maya Jackson-Gibson**[1], Modiegi Diseko[2], Ellen Caniglia[3], Gloria Mayondi[2], Judith Mabuta[2], Rebecca Luckett[4], Sikhulile Moyo[2], Pamela F. Smith-Lawrence[5], Mogomotsi S. Matshaba[6], Mosepele Mosepele[7], Mompati Mmalane[2], Shahin Lockman[8], Joseph Makhema[2], Rebecca Zash[2], Roger L. Shapiro[2]

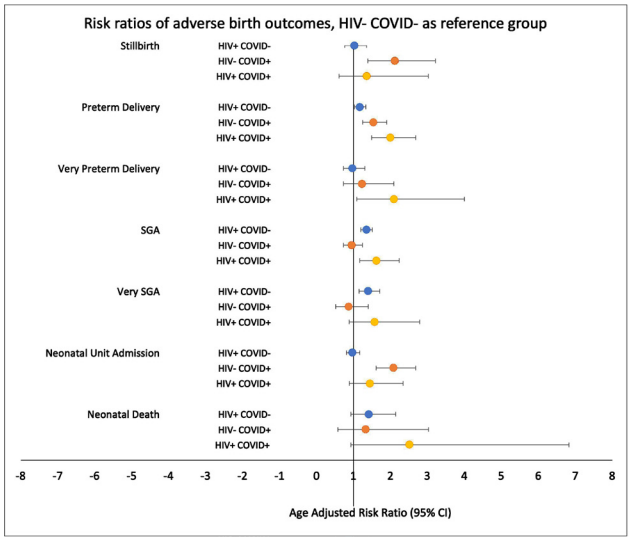
*[1]Northwestern University, Chicago, IL, USA, [2]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [3]University of Pennsylvania, Philadelphia, PA, USA, [4]Beth Israel Deaconess Medical Center, Boston, MA, USA, [5]Botswana Ministry of Health, Gaborone, Botswana, [6]Botswana-Baylor Children's Clinical Centre of Excellence, Gaborone, Botswana, [7]University of Botswana, Gaborone, Botswana, [8]Brigham and Women's Hospital, Boston, MA, USA*

**Background:** Botswana has a high prevalence of women living with HIV (WLHIV) and experienced a severe nationwide COVID-19 epidemic in 2021. We evaluated adverse birth outcomes among women routinely tested for COVID-19 by HIV status, during a period when few women had access to COVID-19 vaccination.

**Methods:** The Tsepamo Study performs birth outcomes surveillance at government hospitals throughout Botswana. We analyzed data from 13 Tsepamo sites that performed routine COVID-19 screening at delivery with rapid antigen or PCR testing between Sept 1, 2020 and Sept 30, 2021 (start dates differed by site). This analysis includes singleton deliveries with known HIV status and a COVID-19 screening test between 14 days prior and 3 days after delivery. Outcomes included maternal death, preterm delivery (PTD), very preterm delivery (VPTD), small for gestational age (SGA), very small for gestational age (VSGA), stillbirth, and neonatal death. Differences in outcomes by COVID-19 and HIV status were assessed using log binomial regression adjusted for maternal age.

**Results:** A total of 17,627 deliveries occurred at the included sites during COVID-19 screening, and 11,149 (63.3%) were screened for COVID-19; among 10,090 (99.7%) with a known HIV status, 530 (5.3%) COVID-19 tests were positive, including 141/2129 (6.6%) among WLHIV and 389/7961 (4.9%) among women without HIV (aRR 1.32, 95% CI 1.09, 1.60). Maternal deaths were reported in 19 (3.8%) women with COVID-19 and 11 (0.12%) women without COVID-19 (aRR 30.5, 95% CI 14.6, 63.7), and did not differ by HIV status. Adverse birth outcomes (any) were more common among infants born to women with COVID-19 (34.3% vs. 26.3%; aRR 1.32, 95% CI 1.16,1.49), including PTD (21.2% vs. 13.3%; aRR 1.60, 95% CI 1.34,1.90) and stillbirth (5.5% vs. 2.8%; aRR 1.89, 95% CI 1.30,2.75), and there was a trend for higher neonatal mortality (2.0% vs. 1.4%, aRR 1.5, 95% CI 0.79, 2.85). Most adverse birth outcomes were highest among infants exposed to both COVID-19 and HIV (Figure 1).

**Conclusion:** Infants born to women with COVID-19 experienced more adverse birth outcomes than other infants, including a 2-fold risk for stillbirth. Those exposed to both COVID-19 and HIV had the highest risk for most adverse outcomes. Further research is warranted to understand the biological interaction between COVID-19, HIV infection, and adverse birth outcomes, and whether some associations were impacted by challenges in care delivery during the height of the COVID-19 epidemic in Botswana.




## 30 GROWTH OF INFANTS WITH PERINATAL EXPOSURE TO MATERNAL DTG VS EFV AND TDF VS TAF

**Lynda Stranix-Chibanda**[1], Lauren Ziemba[2], Sean Brummel[2], Benjamin Johnston[3], Tapiwa G. Mbengeranwa[4], Haseena Cassim[5], Gerhard Theron[6], Sherika Hanley[7], Maxensia Owor[8], Katie McCarthy[9], Nahida Chakhtoura[10], Patrick Jean-Philippe[11], Lameck Chinula[12], Shahin Lockman[13]

*[1]University of Zimbabwe, Harare, Zimbabwe, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Frontier Science Foundation, Inc., Amherst, NY, USA, [4]University of Zimbabwe Clinical Trials Research Centre, Harare, Zimbabwe, [5]Perinatal HIV Research Unit, Soweto, South Africa, [6]Stellenbosch University, Cape Town, South Africa, [7]Centre for the AIDS Programme of Research in South Africa, University of KwaZulu-Natal, Umlazi, South Africa, [8]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [9]FHI360, Durham, NC, USA, [10]National Institute of Child Health and Human Development, Bethesda, MD, USA, [11]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, [12]University of North Carolina Project–Malawi, Lilongwe, Malawi, [13]Brigham and Women's Hospital, Boston, MA, USA*

**Background:** Information is limited about the impact of specific maternal antiretroviral treatment (ART) regimens during pregnancy and breastfeeding on infant growth. Stunting in infancy impacts cognitive development and adult height. We compared infant growth at ~26 and ~50 weeks of age by maternal regimen in a post hoc analysis of the IMPAACT 2010 randomized trial which evaluated three ART regimens in pregnancy.

**Methods:** Pregnant women with HIV in 9 countries were randomized 1:1:1 to start open-label maternal ART with dolutegravir (DTG) plus emtricitabine (FTC)/tenofovir alafenamide (TAF), DTG+FTC/tenofovir disoproxil fumarate (TDF), or efavirenz (EFV)/FTC/TDF at 14-28 weeks' gestation. Mothers and infants were followed through Week 50 postpartum; infant length and weight were measured using standardized procedures. We calculated Z-scores for length-for-age (LAZ), weight-for-age (WAZ), and weight-for-length (WHZ) using WHO standards. Pairwise comparisons of mean LAZ, WAZ, and WHZ used two-sample t-tests at ~26 and ~50 weeks of age. The proportion of infants in each arm with severe stunting (LAZ below -2) was estimated.

**Results:** In predominantly breastfed infants (479/617 [77.6%]) exposed to maternal HIV and ART, mean LAZ and WAZ were lower in the EFV/FTC/TDF arm than the DTG arms. Mean LAZ difference (95% CI) between DTG+FTC/TDF and EFV/FTC/TDF arms was 0.4 (0.1, 0.6; p=0.0056) at Week 26 and 0.3 (0.1, 0.6; p=0.01) at Week 50. Mean WAZ difference (95% CI) between DTG+FTC/TDF and EFV/FTC/TDF arms was 0.3 (0.0, 0.5; p=0.035) at Week 26 and 0.3 (0.1, 0.6; p=0.0094) at Week 50. There were no apparent mean differences between DTG+FTC/TAF and DTG+FTC/TDF arms in LAZ or WAZ at Weeks 26 or 50. Mean WHZ were similar between arms. A lower proportion of infants in the DTG+FTC/TAF and DTG+FTC/TDF arms were severely stunted compared to the EFV/FTC/TDF arm (Table): difference (95% CI) -5.7% (-13.3%, 1.9%) for both arms at Week 26, and -7.2% (-15.0%, 0.7%) and -7.0% (-14.9%, 1.0%) at Week 50, respectively.

**Conclusion:** While infants in the EFV/FTC/TDF arm were smaller than in the DTG arms, growth was similar following exposure to TDF vs. TAF in combination with DTG/FTC. Rates of severe stunting were high across all arms, and present in one in five EFV/FTC/TDF-exposed 1-year old infants. Infant growth should be factored into choice of optimal maternal ART regimen during pregnancy and breastfeeding.

**Table:** Length-for-age mean z-scores and proportion with severe stunting by study arm at Weeks 26 and 50

| | LAZ Mean (SE) | | N severe stunting/total* (%) | |
|---|---|---|---|---|
| | Week 26 | Week 50 | Week 26 | Week 50 |
| DTG+FTC/TAF | -0.7 (0.1) | -0.7 (0.1) | 28/193 (14.5) | 24/179 (13.4) |
| DTG+FTC/TDF | -0.7 (0.1) | -0.6 (0.1) | 28/193 (14.5) | 24/176 (13.6) |
| EFV/FTC/TDF | -1.0 (0.1) | -0.9 (0.1) | 38/188 (20.2) | 35/170 (20.6) |
| Total | -0.8 (0.1) | -0.7 (0.1) | 94/574 (16.4) | 83/525 (15.8) |

*All available data are included in the analysis

## 31 TWO-YEAR VIROLOGIC OUTCOMES OF VERY EARLY ART FOR INFANTS IN THE IMPAACT P1115 STUDY

**Deborah Persaud**[1], Ellen G. Chadwick[2], Bryan S. Nelson[3], Camlin Tierney[3], Mark F. Cotton[4], Anne Coletti[5], Diane Costello[6], Nicol Nicodimus[7], Lynda Stranix-Chibanda[7], Adeodata R. Kekitiinwa[8], Christina Reding[9], Sai Majji[10], Patrick Jean-Philippe[11], Yvonne Bryson[6]

*[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA, [3]Harvard TH Chan School of Public Health, Boston, MA, USA, [4]Stellenbosch University, Stellenbosch, South Africa, [5]FHI 360, Durham, NC, USA, [6]University of California Los Angeles, Los Angeles, CA, USA, [7]University of Zimbabwe, Harare, Zimbabwe, [8]Baylor College of Medicine Children's Foundation, Kampala, Uganda, [9]Frontier Science and Technology Research Foundation, New York, NY, USA, [10]National Institute of Child Health and Human Development, Bethesda, MD, USA, [11]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

**Background:** IMPAACT P1115 assesses very early antiretroviral therapy (ART) for remission of in utero HIV-1 infection. We report on virologic outcomes of very early ART and the potential for HIV-1 reservoir reduction by age 2 years.

**Methods:** 440 high-risk infants (Cohort 1) were enrolled and initiated presumptive nevirapine (NVP)-based ART by age 48 hours; 34 with in utero infection continued ART. An additional 20 infants with in utero infection who had initiated a 3-drug NVP-based regimen by age 48 hours (Cohort 2) were enrolled by age 10 days (Table). Lopinavir/ritonavir was added when age appropriate; NVP was stopped 12 weeks after confirmed HIV-1 plasma viral load (VL) <20 (Roche TQ) or <40 c/mL (Abbot RT). To stay on study, infants had to maintain virologic suppression (VS), defined as VL <200 c/mL at study week 24, <200 c/mL at weeks >24-<48, and no RNA detected at weeks ≥48. Cell-associated HIV-1 DNA (CA-DNA) was measured using a CLIA-certified droplet digital (ddPCR) assay with a lower limit of detection of <4.09 c/106 cells. HIV-1 Ab testing began at week 84. Eligibility for evaluation of remission through ART interruption required maintaining VS, negative HIV-1 antibody (Ab) serostatus, and nondetectable CA-DNA. Estimation included Kaplan-Meier based survival probabilities, exact binomial proportion confidence intervals (CI), and univariate Cox proportional hazards regression (hazard ratio; HR).

**Results:** At week 24, 75% (24/32, 95%CI 57%-89%) in Cohort 1 and 88% (15/17, 64%-99%) in Cohort 2 had VL <200 c/mL. The estimated probability of remaining VS at age 2 years was 33% (17%-49%) in Cohort 1 and 57% (28%-78%) in Cohort 2. In Cohorts 1 and 2, higher earliest CA-DNA load was associated with increased risk of virologic failure (VF) [per $\log_{10}$, HR 1.66 (0.99-2.80) for Cohort 1, 6.80 (1.31-35.20) for Cohort 2]. In Cohort 1, higher earliest VL was associated with increased risk of VF [per $\log_{10}$, 1.64 (1.06-2.53)] and male sex with decreased risk of VF (0.31, 0.11-0.94). In infants with VS through age 2 years, 83% (52%-100%) in Cohort 1 and 100% (59%-100%) in Cohort 2 tested HIV-1 Ab negative; 64% (31%-89%) in Cohort 1 and 71% (29%-96%) in Cohort 2 had nondetectable CA-DNA. The estimated probability of remaining potentially eligible for ART interruption at age 2 years was 33% (21%-46%).

**Conclusion:** Infants with in utero HIV-1 infection who maintain virologic suppression with very early ART can achieve restricted HIV-1 reservoirs by age 2 years, which may enable ART-free remission.

## 32 TREATMENT WITH BROADLY NEUTRALIZING ANTIBODIES IN CHILDREN WITH HIV IN BOTSWANA

**Roger L. Shapiro**[1], Kenneth Maswabi[2], Gbolahan Ajibola[2], Michael Hughes[1], Molly Pretorius Holme[1], Kathleen M. Powis[3], Sikhulile Moyo[2], Bryan S. Nelson[1], Marina Caskey[4], Lucio Gama[5], Patrick Jean-Philippe[5], Dwight E. Yin[5], Edmund Capparelli[6], Daniel Kuritzkes[7], Mathias Lichterfeld[8]

*[1]Harvard TH Chan School of Public Health, Boston, MA, USA, [2]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [3]Massachusetts General Hospital, Boston, MA, USA, [4]The Rockefeller University, New York, NY, USA, [5]National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, [6]University of California San Diego, La Jolla, CA, USA, [7]Brigham and Women's Hospital, Boston, MA, USA, [8]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA*

**Background:** Broadly neutralizing monoclonal antibodies (bNAbs) suppress HIV-1 RNA and may deplete residual viral reservoirs. We evaluated VRC01LS and 10-1074 as a treatment alternative to antiretroviral therapy (ART).

**Methods:** Children who received continuous ART from <7 days (and 1 child with intra-partum infection started at 31 days), and had HIV RNA <40 c/mL for ≥24 weeks prior to entry, enrolled at >96 weeks of age. After at least 8 weeks of overlap with ART (the first 6 participants had 32 wks of overlap during a safety and PK phase), ART was held and treatment with dual VRC01LS and 10-1074 (dosed every 4 wks) was continued. HIV RNA was checked every 1-2 weeks and ART was restarted (and bNAbs discontinued) if >400 c/mL, or at 24 weeks; HIV RNA was checked weekly until <40 c/mL after re-starting ART.

**Results:** Twenty-eight children entered the treatment component of the study while receiving lopinavir/ritonavir-based ART, at a median age of 3.6 (range 2.4, 5.6) years, and median CD4 count 1198 cells/$mm_3$; 25 (89%) went on to the bNAb-only treatment phase (viral rebound occurred in 2 on the day of bNAb initiation and in 1 while on ART and bNAbs). Eleven children (44%, 95%CI 24-65%) maintained HIV RNA <40 c/mL through 24 weeks of bNAb-only treatment (including 1 with a single value of 234 c/mL at wk 16) and after ART re-start. Children with treatment success had favorable pre-intervention clinical and reservoir characteristics (Table 1); 5 of 6 (83%) with long bNAb/ART overlap succeeded. Fourteen children (56%) had viral rebound to >400 c/mL at a median of 4 (range 1, 20) weeks, and were immediately re-started on ART; median HIV RNA at re-start was 4.42 (range 2.87, 6.42) $\log_{10}$ c/mL. After failure, re-suppression to <40 c/mL occurred in all children, at a median of 4.1 (range 0.9-20.3) weeks from ART re-start. No infusion reactions occurred, and bNAbs were well-tolerated with only five grade 3 events (one neutropenia considered possibly study drug-related). PBMC HIV DNA change over time, and neutralization assay data for bNAbs at failure, are forthcoming.

**Conclusion:** In this proof-of-concept study, dual bNAb treatment with VRC01LS and 10-1074 maintained viral suppression for 24 weeks in the absence of ART in 44% of children, and was well-tolerated. Newer bNAb combinations with greater breadth and potency, used in children with favorable pre-treatment characteristics and possibly with longer bNAb/ART overlap, may improve treatment success for this novel ART-sparing strategy.

**Table 1: Characteristics by response group for bNAb-only treatment with VRC01LS and 10-1074 in children living with HIV in Botswana**

| | Treatment Success on bNAbs (N=11)* | Treatment Failure on bNAbs (N=14)* | P-value |
|---|---|---|---|
| **Baseline Characteristics** | | | |
| Median age at ART start | 3 days of life | 2 days of life | 0.12 |
| Median age at bNAb start | 3.28 years | 3.16 years | 0.68 |
| HIV RNA undetectable since 24 wks[%] | 9 (82%) | 4 (29%) | 0.02 |
| Median HIV DNA from PBMCs at start of ART (week 1 of life) | 155 copies/$10^6$ | 784 copies/$10^6$ | 0.02 |
| **Amount of bNAb/ART Overlap** | | | |
| 32 weeks | 5 (83%) | 1 (17%) | 0.06 |
| 8 weeks | 6 (32%) | 13 (68%) | |
| **Median CD4 cell count** | | | |
| Start of bNAb-only treatment | 984 cells/$mm^3$ | 1380 cells/$mm^3$ | 0.05 |
| End of bNAbs (ART re-start or re-suppression[#]) | 1059 cells/$mm^3$ | 1022 cells/$mm^3$ | 0.80 |

* Excludes 3 children who began bNAbs but never discontinued ART.
[%] Defined as all visits at or after 24 weeks of age with HIV RNA <40copies/mL; per protocol, all HIV RNA values in the 24 weeks prior to bNAb initiation must be <40 copies/mL.
[#] Value at ART re-start used for children with treatment success, and value following re-suppression to <40 copies/mL used for children with treatment failure.

## 33 IMPACT OF POINT-OF-CARE HIV VIRAL LOAD TESTING IN KENYAN CHILDREN: A RANDOMIZED TRIAL

**Rena Patel**[1], Patrick Oyaro[2], Katherine K. Thomas[1], James Wagude[3], Irene Mukui[4], Eunice Kinywa[3], Frederick Oluoch[3], Leonard Kingwara[5], Evelyn Brown[6], Enericah C. Kariuki[6], Nashon Y. Odhiambo[6], Grace John-Stewart[1], Lisa Abuogi[7]

*[1]University of Washington, Seattle, WA, USA, [2]Health Innovations Kenya, Kisumu, Kenya, [3]Department of Health, Siaya, Kenya, [4]Kenya Ministry of Health, Nairobi, Kenya, [5]National HIV Reference Lab, Nairobi, Kenya, [6]University of Washington-Kenya, Kisumu, Kenya, [7]University of Colorado Denver, Denver, CO, USA*

**Background:** Kenya has a large burden of pediatric HIV and viral suppression (VS) remains lower among children living with HIV (CLHIV) than adults; feasible, scalable, and cost-effective approaches to ensure VS among CLHIV are urgently needed. The goal of the Opt4Kids study was to determine the impact of point-of-care (POC) viral load (VL) and targeted drug resistance mutation (DRM) testing in improving VS among children on antiretroviral therapy (ART).

**Methods:** We conducted a randomized controlled trial to evaluate the use of POC VL and targeted DRM testing among children aged 1-14 years on ART at five health facilities in western Kenya. Children were randomized 1:1 to intervention (POC VL every 3 months, targeted DRM testing for VL ≥1000 copies/ml, and clinical management support) vs. control (standard-of-care: VL testing every 6 months, DRM restricted to second line ART failure via centralized approvals) groups and followed for 12 months. Our primary outcome was VS (VL <1000 copies/mL) 12 months after enrollment by study group.

**Results:** Of the 704 participants enrolled, the median age at enrollment was 9 years (interquartile range [IQR] 7, 12), 344 (49%) were female, and the median time on ART was 5.8 years (IQR 3.1, 8.6). At 12 months, 90% (283/313) in the intervention group and 92% (287/313) in the control group were virally suppressed (risk ratio (RR) 0.99, 95% confidence interval [CI] 0.94, 1.03). We identified 122 episodes of viremia in intervention participants, of which 107 (88%) samples successfully underwent DRM testing. In contrast, 144 episodes of viremia were identified but only two DRM tests were conducted in the control group. After any non-VS, children were not more likely to achieve VS at 12-months in the intervention vs. control group (RR 1.08, 95% CI 0.92, 1.27). The median turnaround time in days for VL results was 1 (IQR 0, 1) and 14 (IQR 9, 21) in the intervention and control groups, respectively.

**Conclusion:** Overall, VS was high in both groups and was not significantly improved among CLHIV undergoing our intervention of POC VL and targeted DRM testing compared to standard of care. However, VL turnaround time was faster in the intervention group, which could be useful programmatically. Further research is needed to evaluate combination interventions, that best utilize POC VL testing coupled with psychosocial support, to optimize VS for CLHIV.

**Table: Effect of the POC VL and targeted DRM testing on viral suppression at study end and by subgroups among the Opt4Kids study participants (n=704), March 2019- December 2020**

| | Point-of-care viral load results | | | |
|---|---|---|---|---|
| **Variable** | **Intervention (n=349)** | **Control (n=355)** | **Risk Ratio[1] (95% CI)** | ***p*-value** |
| **Primary outcome of viral suppression <1000 copies/mL[3]** (12 months +/- 16 weeks) | 283/313 (90.4%) | 287/313 (91.7%) | 0.99 (0.94, 1.03) | 0.550 |
| **Secondary outcome of viral suppression <40 copies/mL[3]** (12 months +/- 16 weeks) | 236/313 (75.4%) | 229/313 (73.1%) | 1.03 (0.94, 1.13) | 0.567 |
| **Primary outcome[3] by baseline subgroup** | | | | |
| Sex | | | | 0.922 |
| Female | 146/164 (89.0%) | 128/143 (89.5%) | 0.99 (0.92, 1.07) | |
| Male | 137/149 (92.0%) | 159/170 (93.5%) | 0.99 (0.93, 1.05) | |
| Age | | | | 0.272 |
| 1-9 years | 169/187 (90.4%) | 176/196 (89.8%) | 1.01 (0.94, 1.08) | |
| 10-14 years | 114/126 (90.5%) | 111/117 (94.9%) | 0.95 (0.89, 1.02) | |
| Time on ART | | | | 0.067 |
| < 2 year | 37/48 (77.1%) | 38/42 (90.5%) | 0.85 (0.71, 1.02) | |
| 2 – 5 years | 73/78 (93.6%) | 75/86 (87.2%) | 1.07 (0.97, 1.19) | |
| > 5 years | 173/187 (92.5%) | 174/185 (94.1%) | 0.98 (0.93, 1.04) | |
| Viral suppression status of caregiver | | | | 0.144 |
| Yes | 181/196 (92.4%) | 179/199 (90.0%) | 1.02 (0.96, 1.09) | |
| No | 35/43 (81.4%) | 27/28 (96.4%) | 0.85 (0.72, 0.99) | |
| Not available | 20/22 (90.9%) | 16/17 (94.1%) | 0.96 (0.81, 1.15) | |
| HIV-1 negative or unknown | 47/52 (90.4%) | 65/69 (94.2%) | 0.96 (0.86, 1.07) | |
| Caregiver biologic parent | | | | 0.806 |
| Yes | 222/246 (90.2%) | 219/240 (91.3%) | 0.99 (0.93, 1.05) | |
| No | 61/67 (91.0%) | 68/73 (93.2%) | 0.97 (0.88, 1.07) | |

Abbreviations: VL=viral load; POC=point-of-care; SOC=standard-of-care; ART=antiretroviral therapy; DRM=drug resistance mutation

[1] Risk ratios, confidence intervals, and *p*-values generated by Poisson regression modified with robust standard error estimation, and adjusted for facility and age group strata, except for the analyses within age group, which are adjusted only for facility. *P*-values indicate statistical significance of the effect of the intervention, except for *p*-values for subgroup analyses which are the *p*-value for the interaction term between the subgroup variable and intervention effect and indicate whether the estimates for the RR differ by subgroup status.

## 34 GEOGRAPHICAL DIFFERENCES IN FUNCTIONAL IMPAIRMENT OF PEOPLE WITH HIV

**Kristine Erlandson**[1], Kathleen Fitch[2], Sara McCallum[2], Heather J. Ribaudo[2], Edgar T. Overton[3], Gerald S. Bloomfield[4], Todd Brown[5], Carl J. Fichtenbaum[6], Sara Bares[7], Judith A. Aberg[8], Pamela S. Douglas[9], Laura Moran[10], Vidya Mave[11], Steven Grinspoon[2]

*[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Harvard Medical School, Boston, MA, USA, [3]University of Alabama at Birmingham, Birmingham, AL, USA, [4]Duke Global Health Institute, Durham, NC, USA, [5]The Johns Hopkins University, Baltimore, MD, USA, [6]University of Cincinnati, Cincinnati, OH, USA, [7]University of Nebraska Medical Center, Omaha, NE, USA, [8]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [9]Duke Clinical Research Institute, Durham, NC, USA, [10]Social & Scientific Systems, Silver Spring, MD, USA, [11]Byramjee Jeejeebhoy Government Medical College, Pune, India*

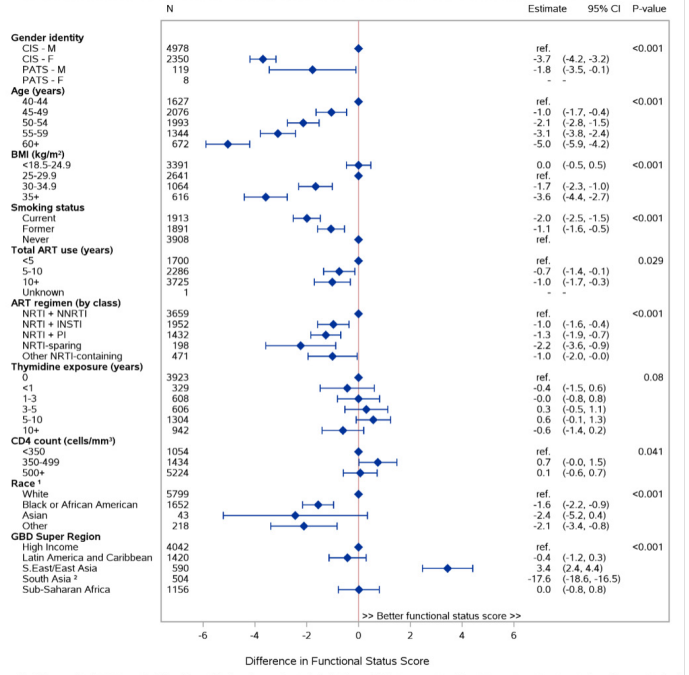
**Background:** Functional impairments occur at a younger age among people with HIV (PWH). However, studies to date have not compared differences in functional impairment across diverse regions in a global HIV cohort. We sought to explore multinational differences by Global Burden of Disease (GBD) regions in functional status and associated factors in the REPRIEVE cohort.

**Methods:** REPRIEVE is a prospective, double-blind, randomized, placebo-controlled, multicenter, phase III primary cardiovascular prevention study of pitavastatin calcium vs placebo among PWH ages 45-75 on antiretroviral therapy (ART). GBD super regions were defined using World Health Organization classifications. The Duke Activity Status Instrument (DASI) estimates functional capacity by metabolic equivalents and was administered at baseline. Participants were categorized by impairment: none, some, moderate, severe. Linear regression models examined risk factors and GBD regions associated with functional impairment. We also explored the association between function impairment and cardiometabolic risk.

**Results:** Of 7736 participants, the majority were from high-income countries (n=4065), CD4 counts ≥500 cells/uL (68%), and using ART for ≥ ten years (48%); 35% were female. The median DASI score was 58.2 (IQR 50.2, 58.2); 36% reported at least some impairment. Functional status scores and degree of impairment differed across GBD region, with the lowest scores (greatest impairment) reported in South Asia (mean [sd] 37.7 [10.3]) and the highest scores (least impairment) in Southeast/East Asia (mean [sd] 57.3 [3.9]). In adjusted analyses, functional impairment was significantly more frequent among participants from Southeast/East Asia. Other factors associated with greater impairment included female sex, older age, Black race, current/former smoking, higher body mass index, use of ART for ≥ 10 years, and select ART regimens (Figure). Lastly, moderate-severe functional impairment was associated with a small (0.5 point) but significantly greater ASCVD risk score and a 1.45 greater odds of having metabolic syndrome (95% CI 1.20-1.77).

**Conclusion:** Over 1/3 of middle-aged and older PWH in a global cohort across diverse GBD regions demonstrate functional impairments, associated with numerous modifiable and non-modifiable factors. The associations between DASI and cardiometabolic risk suggest that a measure of functional status may improve risk prediction.

**Multivariate Associations Between Demographic and HIV-related Factors with Functional Status**




*Alcohol use and Nadir CD4 count (cells/mm³) - not displayed - were also included in the model, but were not significant. Parameter estimates not shown for covariate levels with sample size <10. [1]In the adjusted analysis, race effect estimated within High income region only due to limited racial variability in other regions; the GBD region effects thus reflect differences compared to white race within the High income region. [2]The estimate and confidence interval exceeds the plottable area.*

## 35 ANTICHOLINERGIC MEDICATIONS ASSOCIATED WITH FALLS AND FRAILTY IN PEOPLE WITH HIV

**Jessica Doctor**[1], Alan Winston[2], Jaime Vera[3], Frank A. Post[4], Marta Boffito[5], Patrick Mallon[6], Jane Anderson[7], Margarita Durkina[2], Ian Williams[1], Margaret Johnson[8], Manolis Bagkeris[1], Memory Sachikonye[9], Caroline Sabin[1]

*[1]University College London, London, UK, [2]Imperial College London, London, UK, [3]Brighton and Sussex Medical School, Brighton, UK, [4]King's College Hospital, London, UK, [5]Chelsea and Westminster Hospital, London, UK, [6]University College Dublin, Dublin, Ireland, [7]Homerton University Hospital NHS Trust, London, UK, [8]Royal Free Hospital, London, UK, [9]UK Community Advisory Board, London, UK*

**Background:** Anticholinergic medications (ACMs) are associated with poorer age-related outcomes including falls and frailty. Drug interactions and comorbidities may increase the risk of ACM use in people with HIV (PWH). We

investigate the associations of ACM use with falls and frailty among older (>50 years) PWH participating in the POPPY study.

**Methods:** The anticholinergic potential of all co-medications received at POPPY entry was coded using the anticholinergic burden score (ACB), anticholinergic risk score (ARS) and Scottish Intercollegiate Guidelines Network (SIGN) score; drugs scoring ≥1 on any of the scales were defined as ACM. Associations with recurrent falls (≥2 self-reported falls in 28 days) and frailty (modified Fried's, ≥3 of low grip strength, low gait speed, self-reported exhaustion and low activity) were assessed using univariate and multivariable logistic regression adjusting for 1) demographic/lifestyle factors only, and additionally 2) number of non-ACM co-medications, comorbidities and depressive symptoms (PHQ-9).

**Results:** The 699 PWH had a median age of 57 years (interquartile range 53-62), 88% were male, 86% White, 60% single and 34% unemployed or sick/disabled. Almost all (692, 99%) were on antiretroviral therapy, 642 (92%) had viral load <50 cps/ml and 607 (89%) CD4>350 cells/mm$_3$. ACM use was reported by 193 (28%) with 64 (9%) on ≥2 ACM; commonly prescribed ACM were codeine (12%), citalopram (12%), loperamide (9%), amitriptyline (7%) and diazepam (6%). Those on ACM were more likely to be White (92% vs 84%, p=0.005), single (69% vs 60%, p=0.02), sick/disabled (30% vs 15%, p<0.001) and report recent recreational drug use (31% vs 23%, p=0.05) than non-ACM users. Falls were reported in 63/673 (9%) and 126/609 (21%) met frailty criteria. Those reporting ACM use were more likely to report falls (17% vs 6% in non-ACM users, p<0.001) and frailty (32% vs 17%, p<0.001). Use of ≥2 ACMs was associated with an increased odds of falling after adjustment for confounders (demographic/lifestyle factors only: odds ratio 4.53 [95% confidence interval 2.06-9.98]); +clinical factors (3.58 [1.37-9.38]) (Table). Similar, although weaker, associations were seen with frailty (2.26 [1.09-4.70] and 2.12 [0.89-5.0], respectively).

**Conclusion:** ACM are commonly prescribed for PWH. There is strong evidence for an association between cumulative ACM use and recurrent falls, and to a lesser extent frailty. Clinicians should be alert to this association and reduce ACM exposure where possible.

**Table. Results from univariate and multivariable logistic regression analyses to determine associations between use of ≥2 ACMs and i) recurrent falls, and ii) frailty**

| Adjustment | | Falls | | | Frailty | | |
|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | P value | OR | 95% CI | P value |
| Unadjusted | No ACM | 1 | - | | 1 | - | |
| | 1 | 2.09 | 1.03- 4.23 | | 1.93 | 1.16-3.20 | |
| | ≥2 | 6.83 | 3.31-14.11 | <0.001 | 3.33 | 1.71-6.47 | 0.001 |
| Demographic/lifestyle factors only[1] | No ACM | 1 | - | | 1 | - | |
| | 1 | 1.67 | 0.79-3.49 | | 1.62 | 0.93-2.82 | |
| | ≥2 | 4.53 | 2.06-9.98 | 0.001 | 2.26 | 1.09-4.70 | 0.04 |
| Demographic/lifestyle factors plus clinical factors[2] | No ACM | 1 | - | | 1 | - | |
| | 1 | 1.43 | 0.63-3.25 | | 1.52 | 0.82-2.84 | |
| | ≥2 | 3.58 | 1.37-9.38 | 0.03 | 2.12 | 0.89-5.02 | 0.17 |

[1]age, work, marital status and recent recreational drug use; [2]additionally adjusted for number of non ACM co-medications, number of comorbidities and PHQ-9 score.

## 36 INFLAMMATION AND KYNURENINE PATHWAY LINKED TO TYPE 2 DIABETES AND FAT FIBROSIS IN HIV

**Diana L. Alba**[1], Samuel R. Schnittman[2], Rachel T. Cheang[1], Gabriele B. Beck-Engeser[1], Fay Chan[1], Dave Glidden[1], Joseph A. Delaney[3], Amelia N. Deitchman[1], Fran Aweeka[1], Judy K. Shigenaga[1], Carl Grunfeld[1], Heidi Crane[4], Suneil K. Koliwad[1], Peter W. Hunt[1]

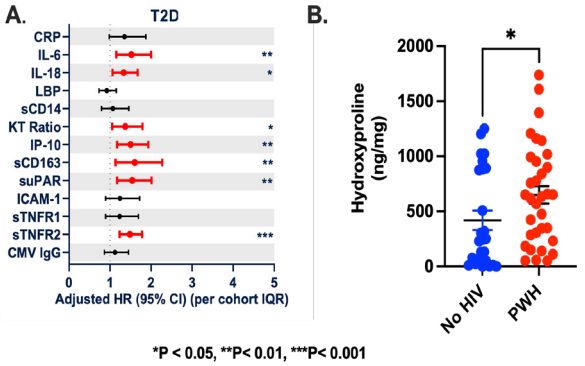
*[1]University of California San Francisco, San Francisco, CA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]University of Manitoba, Winnipeg, Canada, [4]University of Washington, Seattle, WA, USA*

**Background:** People with HIV (PWH) are at increased risk for type 2 diabetes (T2D), which has been linked to persistent inflammation despite ART. PWH have also been reported to have increased adipose tissue fibrosis, which has also been linked to insulin resistance, but the inflammatory pathways most closely linked to incident T2D and adipose tissue fibrosis in this setting remain unclear.

**Methods:** To assess immunologic predictors of incident T2D, we randomly sampled CNICS participants without prevalent diabetes but with available plasma after 1 year of suppressive ART and assessed the relationship between 13 plasma biomarkers normalized to the cohort interquartile range (IQR) and incident T2DM with Cox models adjusted for age, natal sex, nadir CD4, and other potential confounders (smoking, IDU, and HCV history). Separately, we assessed the relationship between the same plasma markers and insulin resistance (HOMA-IR) and the fibrosis marker hydroxyproline in subcutaneous adipose tissue (SAT) aspirates in ART-suppressed PWH and those without HIV, all without T2D and frequency matched by HgA1c in the SCOPE cohort.

**Results:** Among 843 ART-suppressed CNICS participants, there were 97 incident T2D cases. Median age was 46, 84% were men, and 16% had a history of HCV. Median current and nadir CD4 were 571 and 250. Higher IL-6, IL-18, IP-10, sCD163, suPAR, sTNFR2 and kynurenine-to-tryptophan (KT ratio) were associated with incident T2D (Figure). The adipose tissue sampling study included 41 PWH and 30 sero-negative participants, 68% men, with median values: age, 50; BMI, 28; HgA1c, 5.4. Compared to those without HIV, PWH had higher SAT levels of the fibrosis marker hydroxyproline (P=0.03) and higher plasma KT ratio (P=0.03). While most inflammatory markers predicted HOMA-IR in PWH, KT ratio was the most strongly correlated with adipose tissue hydroxyproline levels (rho: 0.31, P=0.04). Adjustment for KT ratio also significantly attenuated the difference in hydroxyproline levels between people with and without HIV (P=0.35).

**Conclusion:** Many inflammatory pathways, including the kynurenine pathway of tryptophan catabolism, predict incident T2D in treated HIV infection. PWH also have abnormally high SAT fibrosis, which is also associated with the kynurenine pathway. As the kynurenine pathway has been linked to Treg expansion and fibrotic pathways in prior studies, these data may suggest a potential role of this pathway in subcutaneous adipose tissue fibrosis and insulin resistance in treated HIV.




*P < 0.05, **P< 0.01, ***P< 0.001

## 37 GUT MICROBIOTA, PLASMA METABOLOMICS, AND ATHEROSCLEROSIS IN HIV INFECTION

**Zheng Wang**[1], Wendy Post[2], Alan Landay[3], Kathleen Weber[4], Elizabeth T. Golub[5], Deborah Gustafson[6], Seble Kassaye[7], Bradley Aouizerat[8], Sabina Haberlen[9], Carlos Malvestutto[10], Matthew Budoff[11], Kathryn Anastos[1], Robert Kaplan[1], Robert Burk[1], Qibin Qi[1]

*[1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]Rush University Medical Center, Chicago, IL, USA, [4]Hektoen Institute of Medicine, Chicago, IL, USA, [5]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [6]State University of New York-Downstate Medical Center, Brooklyn, NY, USA, [7]Georgetown University, Washington, DC, USA, [8]New York University, New York, NY, USA, [9]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [10]Ohio State University, Columbus, OH, USA, [11]University of California Los Angeles, Los Angeles, CA, USA*

**Background:** Alterations in gut microbiota and blood metabolomic profiles have been implicated in HIV infection and cardiovascular disease respectively. However, it remains unclear whether alterations in gut microbiota and related functional components may contribute to disrupted host blood metabolomic profiles in relation to atherosclerosis, especially in the context of HIV infection.

**Methods:** We analyzed cross-sectional associations between gut microbiota features (eg, diversity and taxonomy) and carotid artery plaque in 361 women with or at high risk of HIV (67% HIV+) from the Women's Interagency HIV Study(WIHS). We further examined cross-sectional associations of gut bacterial genera and functional enzymes with plasma lipidomic and metabolomic profiles. In 737 women and men from the WIHS and the Multicenter AIDS Cohort Study, we examined prospective associations of baseline gut bacteria-associated lipidomic and metabolomic profiles with incident carotid artery plaque over a median 7-year follow-up.

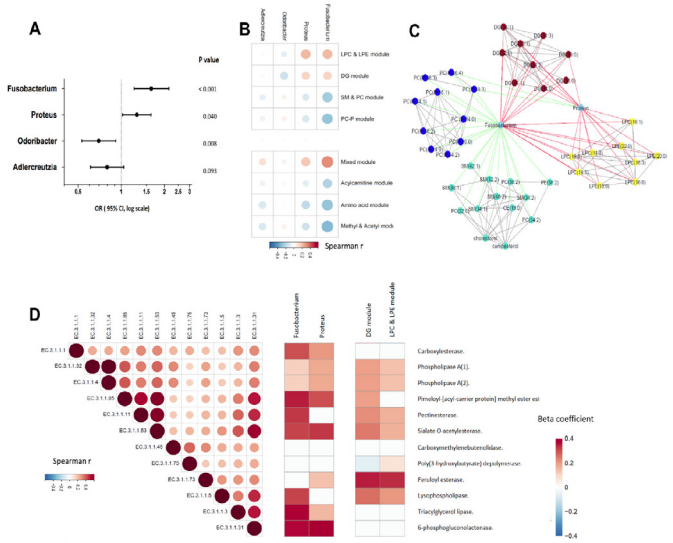
**Results:** Two potentially pathogenic bacteria, Fusobacterium and Proteus, were positively associated with carotid artery plaque, while two bacteria which can produce beneficial metabolites (eg, butyrate), Odoribacter and Adlercreutzia, were inversely associated with carotid artery plaque (Fig 1A). Gut Fusobacterium and Proteus, but not Odoribacter or Adlercreutzia, were associated with multiple plasma lipids and metabolites, and these lipids and metabolites were

clustered into 8 modules by the network analysis (Fig 1B,C). A module comprised of 9 lysophosphatidylcholines(LPCs) and lysophosphatidylethanolamines(LPEs) and a module comprised of 9 diglycerides (DGs) were longitudinally associated with increased risk of carotid artery plaque (RR[95% CI] = 1.34[1.09, 1.64] and 1.24[1.02, 1.51] per SD increment in the module scores, respectively). Functional analyses identified several bacterial enzymes in the lipid metabolism associated with the above plasma lipids as well as gut Fusobacterium and Proteus (Fig 1D). In particular, phospholipase A1 and A2 are the key enzymes in the reactions producing LPCs and LPEs from phosphatidylcholines and phosphatidylethanolamines.

**Conclusion:** Among individuals with or at high risk of HIV infection, we identified altered gut microbiota and related functional capacities in the lipid metabolism associated with disrupted plasma lipidomic profiles and carotid artery atherosclerosis.

**Figure 1. Associations among gut microbiota taxa, microbial functional components, plasma lipidomic and metabolomic profiles, and carotid artery atherosclerosis**

(A) Associations between genera and plaque status. Data are odds ratios (ORs) and 95% confidence intervals (CIs) for carotid artery plaque per standard deviation increment of CSS transformed abundance of gut bacterial genera, adjusting for age, race, study site, antibiotics use, income, education, BMI, current smoking status, marijuana use and HIV status.
(B) Correlations between bacterial genera and the 8 modules of lipids and metabolites.
(C) Network plot illustrating the *Fusobacterium* and *Proteus* correlated lipids modules. The color of node reflects the module of each metabolites and the grey edges indicate the weighted correlation coefficients among metabolites. Red/green lines indicate the significant positive/inverse correlations between bacterial genera and metabolites.
(D) The correlation heatmap include 12 microbial functional enzymes under carboxylic-ester hydrolases category. Associations between these enzymes and the plaque-related bacterial genera *Fusobacterium*/*Proteus*, as well as the lipidomics DG module and LPC & LPE module, were estimated by linear regression models after adjustment for aforementioned covariates.
Abbreviations: LPC, lysophosphatidylcholine ; LPE, lysophosphatidylethanolamine; DG, diglyceride; SM, Sphingomyelin; PC, phosphatidylcholine; PC-P, phosphatidylcholines plasmalogen.




## 38 MACROPHAGE ARTERIAL INFILTRATION RELATES TO PLAQUE TYPE AND IMMUNE ACTIVATION IN HIV

**Mabel Toribio**[1], Moses Wilks[1], Sandeep Hedgire[1], Michael T. Lu[1], Madeline Cetlin[1], Melissa Wang[1], Iad Alhallak[1], Kevin S. White[2], Zoey K. Wallis[2], Takara Stanley[1], Georges El-Fakhri[1], Patrick Autissier[1], Markella V. Zanni[1], Kenneth Williams[2], Steven Grinspoon[1]
*[1]Massachusetts General Hospital, Boston, MA, USA, [2]Boston College, Chestnut Hill, MA, USA*

**Background:** Persistent immune activation and downstream macrophage-specific arterial infiltration are thought to contribute to heightened atherosclerotic cardiovascular disease (ASCVD) risk among people with HIV (PWH) on ART. We applied a novel macrophage-specific imaging modality to investigate macrophage-specific infiltration among participants with vs without HIV in relation to atherosclerotic plaque and immune activation.

**Methods:** Twenty PWH on ART and 10 participants without HIV underwent systemic administration of the CD206 macrophage-specific radiotracer, 99mTc-tilmanocept, followed by SPECT/CT imaging to assess arterial inflammation. Participants were ≥18 yrs and without a history of symptomatic ASCVD. The volume of aortic tilmanocept uptake that was 3-6x background muscle activity (signal to background ratio, SBR) was measured. Aortic plaque volumes [total, non-calcified (Hounsfield units (HU) <130 and HU <300), and calcified plaque (HU≥130 and HU≥300)] were quantified using cardiac CT.

**Results:** Participants with vs without HIV were similar in age (55.1 vs 58.4 yrs, P=0.12) and 10-yr ASCVD risk (7.3 vs. 8.1, P=0.70). Total, non-calcified, and calcified aortic plaque volume did not differ significantly between groups. Systemic markers of immune activation (caspase-1: P=0.01, MCP-1: P=0.02, and CXCL10: P=0.0004) and non-classical/homing monocytes (CD14-CD16+: P=0.02) were higher among PWH. Aortic tilmanocept uptake was higher across different uptake thresholds among PWH (P=0.03; Fig 1a-b). There was a significant interaction between HIV status and plaque volume in relation to arterial inflammation for non-calcified plaque (P=0.0001, Fig 1c) but not with calcified plaque (P=0.83) with significant relationships between non-calcified aortic plaque volume with each tilmanocept uptake threshold for PWH but not participants without HIV (Fig 1d). Markers of immune activation (sCD163 P=0.045 and caspase-1, P=0.02), immune cell subpopulations (CD14+CD16- P=0.0001, CD14+CD16+, P=0.02 and CD8+ T-cells P=0.01), and CD4+/CD8+ ratio (P=0.02) related to aortic tilmanocept uptake volume among PWH but not among participants without HIV.

**Conclusion:** These data applying a novel imaging modality provide unique evidence of macrophage-specific arterial inflammation among PWH on ART, which relates specifically to non-calcified plaque. Additionally, we characterize key immune pathways relating to increased arterial inflammation of relevance to identifying novel immunomodulatory therapies for CVD reduction.

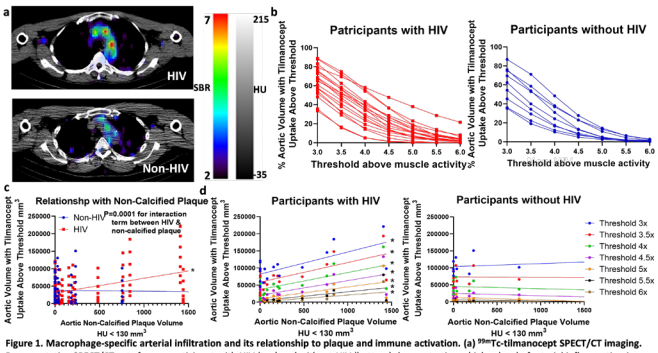



**Figure 1. Macrophage-specific arterial infiltration and its relationship to plaque and immune activation. (a) $^{99m}$Tc-tilmanocept SPECT/CT imaging.** Representative SPECT/CT cuts from a participant with HIV (top) and without HIV (bottom) demonstrating a higher level of arterial inflammation in HIV. **(b) Arterial inflammation at thresholds above background (signal to background ratio).** Higher aortic tilmanocept uptake across different thresholds in HIV (P=0.03). **(c) Arterial inflammation and aortic plaque type.** Significant interaction between HIV-status and aortic plaque volume across different thresholds for non-calcified plaque (P=0.0001 for interaction; $R^2$=0.19, P<0.0001) but not for calcified plaque (P=0.83 for interaction; $R^2$=0.0003, P=0.90). **(d) Arterial inflammation and non-calcified plaque volume.** Among participants with HIV (but not participants without HIV), arterial inflammation related significantly to aortic non-calcified plaque volume across different thresholds. Sensitivity analyses excluding participants with plaque volume > 1000mm$^3$ remained significant. *** P<0.05.**

## 39 TRENDS IN MYOCARDIAL INFARCTION RISK BY HIV STATUS IN 2 US HEALTHCARE SYSTEMS

**Michael J. Silverberg**[1], Asya Lyass[2], Leo Hurley[1], Rachel Ehrbar[2], Taylor Mahoney[3], Leila Borowsky[4], Wei He[5], Jorge Plutzky[6], Daniel Klein[1], Joseph M. Massaro[7], Ralph B. D'Agostino Sr[2], Virginia A. Triant[4]
*[1]Kaiser Permanente Division of Research, Oakland, CA, USA, [2]Boston University, Boston, MA, USA, [3]Babcock University, Remo, Nigeria, [4]Massachusetts General Hospital, Boston, MA, USA, [5]Boston University School of Public Health, Boston, MA, USA, [6]Brigham and Women's Hospital, Boston, MA, USA, [7]Boston Children's Hospital, Boston, MA, USA*

**Background:** With the potential adverse cardiovascular effects of newer antiretroviral therapy (ART), such as integrase inhibitors and weight gain and Tenofovir Alafenamide and elevated lipids, it is critical to continue monitoring trends in myocardial infarction (MI) rates by HIV status.

**Methods:** Subjects included people with HIV (PWH) from two health system cohorts: Massachusetts General Hospital (Partners) and Kaiser Permanente Northern California (KPNC), identified from 2005-2017 with follow-up through 2020. Subjects also included a 1:4 propensity-matched comparison group of people without HIV (PWoH) in Partners and a 1:2 matched group in KPNC. Propensity scores were informed by baseline demographics (age, race, sex, year) and baseline Framingham risk score components (total cholesterol, HDL, diabetes, systolic BP, hypertension treatment and smoking status). We assessed effect of HIV status on MI risk in two calendar eras defined by baseline year: 2005-2009 and 2010-2017. To ensure similar follow-up of events by era, we censored follow-up at the earliest of: 5 years after baseline, death, loss-to-follow-up, or administrative end of follow-up. We used Cox Proportional Hazards models to obtain adjusted HRs of effect of HIV status on MI (PWoH as reference) overall, and by cohort. We obtained two adjusted models: (1) adjusted for age and sex only; and (2) stepwise model adjusted for demographics and Framingham risk score components.

**Results:** We included 10,312 PWH and 23,018 PWoH, of whom 238 had an MI. Mean age of the combined cohort was 43 years, 87% were men, mean cholesterol of 180 mg/dL, mean HDL of 44 mg/dL, 6% diabetes, mean systolic BP of 123 mmHg, 25% on treatment for hypertension, and 26% were smokers. The cohorts were similar except for more men (90% vs. 76%), fewer on treatment for hypertension (24% vs. 30%) and fewer smokers (23% vs. 40%) in KPNC vs. Partners. In the stepwise models for the overall cohort (Table), the HR for MI was 0.99 (0.67, 1.45) for years 2005-2009 and 1.85 (1.26, 2.72) for years 2010-2017, with a corresponding P-interaction of 0.039. The magnitude of HRs by calendar era was consistent across models stratified by cohort.

**Conclusion:** Data from two distinct US cohorts suggest increased MI risk among PWH in recent years. In light of known metabolic effects of newer ART regimens, continued surveillance for MIs is warranted.

Adjusted HRs (95% CI; p-value) for HIV status effect on MI risk (PWoH reference) within calendar eras, overall and by cohort

| Calendar era | Overall N= 33,330 (31% PWH) | Partners N=6,032 (20% PWH) | Kaiser Permanente N=27,298 (33% PWH) |
|---|---|---|---|
| | Age- and sex-adjusted models | | |
| 2005-2009 | 0.97 (0.66, 1.42; p=0.87) | 1.13 (0.24, 5.35; p=0.88) | 0.88 (0.59, 1.31; P=0.52) |
| 2010-2017 | 1.74 (1.18, 2.57; p=0.005) | 1.78 (0.50, 6.31; p=0.38) | 1.73 (1.15, 2.60; p=0.009) |
| | Stepwise adjusted models | | |
| 2005-2009 | 0.99 (0.67, 1.45; p=0.95) | 1.06 (0.22, 5.00; p=0.94) | 0.87 (0.59, 1.30; p=0.51) |
| 2010-2017 | 1.85 (1.26, 2.72; p=0.002) | 2.09 (0.57, 7.65; P=0.26) | 1.82 (1.21, 2.73; P=0.004) |

## 40 NONSMALL CELL LUNG CARCINOMA IN PLWH HARBORS IMMUNOREGULATORY TUMOR MICROENVIRONMENT

New Investigator Scholar

**Syim Salahuddin**[1], Ramsey Yusuf[1], Shruti Desai[1], Kishu Ranjan[1], Jianlei Gu[2], Daiwei Tang[2], Yong Kong[2], Hongyu Zhao[2], Yuval Kluger[1], Kurt Schalper[1], Brinda Emu[1]

*[1]Yale School of Medicine, New Haven, CT, USA, [2]Yale School of Public Health, New Haven, CT, USA*

**Background:** Non-small cell lung carcinoma (NSCLC) is increased in incidence and a leading cause of cancer death among people living with HIV (PLWH). We explored whether HIV-associated immunologic changes results in an immunoregulatory tumor microenvironment (TME) with limited tumor-specific responses among PLWH.

**Methods:** A tissue microarray was constructed with tumors from 18 HIV+ and 19 HIV- NSCLC patients (matched for histology, stage, year of diagnosis, age, sex and smoking status), and incubated with metal-conjugated antibodies for evaluation by imaging mass cytometry (IMC). IMC marker scores were extracted by automated cell segmentation and single-cell data was analyzed by Phenograph. In addition, whole exome sequencing was performed on tumor tissue.

**Results:** HIV+ and HIV- tumors demonstrated differential distribution of tumor-infiltrating CD8+ T cell clusters defined by marker expression patterns. Two clusters were significantly elevated in HIV+ tumors (20.3% and 19.9% vs. 9.2% and 4.7% in HIV- tumors, p<0.0001 for both). The first cluster exhibited an activated effector memory phenotype (CD45RO+CD25+). The second cluster resembled a previously described effector burned-out "Ebo" CD8+ T cell subset with co-expression of immune checkpoint and proliferation markers (PD-1+LAG-3+Ki67+). Within tumor-infiltrating CD4+ T cells, a cluster characterized by checkpoint protein expression (PD-1+ and LAG-3) was also highly represented in HIV+ cases (35.2% vs. 9.8% in HIV- cases, p<0.0001). Finally, HIV+ tumor-associated macrophages (TAM) had higher expression of immunoregulatory molecules (PD-L1, PD-L2, B7-H3, B7-H4, IDO1 and VISTA), confirmed by the expansion of three clusters comprising 58.8% of TAMs vs. 17.8% in HIV- tumors (p<0.0001). Discrimination of cells between HIV+ and HIV- TME was further confirmed by spectral graph theory. Furthermore, tumor mutational burden and neoantigen calling was higher among HIV+ tumors suggesting more antigenic tumors among PLWH.

**Conclusion:** Our study suggests that the TME of HIV+ patients is characterized by a unique immune landscape, distinct from that of HIV- patients, with evidence of expansion of immune cells with enhanced immunoregulatory phenotypes and associated with impaired anti-tumor responses. These differences may be due to long-standing viral replication and destruction of lymphoid architecture. Further studies are necessary to elucidate the impact of these findings on prognosis and response to treatment, particularly checkpoint inhibitor-based approaches.

## 41 HPV GENOTYPING IN STUDY OF ADJUNCTIVE VACCINE FOR TREATMENT OF CERVICAL DYSPLASIA

**Grant Ellsworth**[1], Yvonne Perner[2], Mathilda Claaseen[3], Avril J. Swarts[2], Vuyokazi Jezile[2], Masangu Mulongo[4], Bridgette Goeieman[5], Sophie Williams[5], Mark Faesen[5], Pamela Michelow[2], Wolfgang Preiser[3], Timothy Wilkin[1], Cynthia S. Firnhaber[6]

*[1]Weill Cornell Medicine, New York, NY, USA, [2]University of the Witwatersrand, Johannesburg, South Africa, [3]Stellenbosch University, Cape Town, South Africa, [4]University of Witwatersrand, Johannesburg, South Africa, [5]Helen Joseph Hospital, Johannesburg, South Africa, [6]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** Women with HIV have higher rates of cervical cancer, cervical high grade squamous intraepithelial lesions (HSIL) and HSIL recurrence after treatment compared to the general population. A randomized study of adjuvant quadrivalent HPV vaccine (qHPV) in South African women with HIV undergoing loop electrosurgical excision procedure (LEEP) did not improve HSIL outcomes. We sought to understand if HPV genotyping of observed HSIL to further understand the trial outcomes.

**Methods:** Women with cervical HSIL received qHPV at weeks 0, 4, and 26 and were treated with LEEP at week 4. All formalin-fixed paraffin embedded LEEP (week 4) specimens and recurrent cervical HSIL specimens from (weeks 26 and/or 52) were genotyped using the Atila Ampfire High Risk HPV Genotyping Assay. HPV genotypes in Week 4 LEEP specimens were related to HSIL recurrence and differences in HPV genotypes detected in recurrent HSIL specimens were compared between arms.

**Results:** 164 of 180 LEEP specimens had available samples and successful HPV genotyping. 46 (28%) of LEEP specimens contained HPV 16 and/or 18, 96 (59%) of LEEP specimens contained HPV types covered by the nine-valent HPV vaccine (9vHPV), and 119 (67%) had any high-risk HPV detected. Histologic HSIL recurrence after LEEP was associated with detection of HPV other than HPV 16 or 18 in the LEEP specimens when adjusted for positive LEEP margin (adjusted OR 2.9; 95% CI 1.3-6.2; p<0.01). HPV 16 and/or 18 were detected in 7 (37%) of placebo arm and 4 (18%) of qHPV arm of the week 26 specimens, HPV 16 and/or 18 were also detected 1 (13%) of each arm of the week 52 specimens. Overall there were no differences in HPV genotypes in recurrent specimens attributable to study treatment assignment (see Figure).

**Conclusion:** Only a minority of cervical HSIL was due to qHPV types which may have contributed to the lack of efficacy of qHPV to prevent recurrent HSIL. Adjunctive 9vHPV vaccine may offer more protection against recurrent HSIL. However, no differences were observed by arm of in the small numbers of recurrent HSIL secondary to HPV 16 and/or 18.

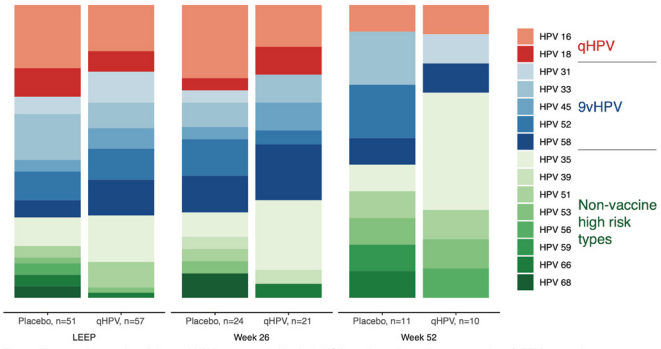



Figure. The overall proportion of detected HPV genotypes in histologic HSIL specimens by study arm at weeks 4 (LEEP), 26, and 52. Reds = qHPV vaccine types. Blues = 9vHPV vaccine types other than HPV 16 and 18. Greens = Non-vaccine high-risk HPV types in genotyping assay. qHPV = quadrivalent HPV vaccine. 9vHPV = nine valent HPV vaccine.

## 42 ANGIOGENIC FACTORS IN RNA-SEQ OF SKIN AND GASTROINTESTINAL KAPOSI SARCOMA LESIONS

**Ramya Ramaswami**[1], Takanobu Tagawa[1], Anna Serquina[1], Guruswamy Mahesh[1], Xiaofan Li[1], Vishal Koparde[1], Kathryn Lurain[1], Ralph Mangusan[1], Anaida Widell[1], Irene Ekwede[1], Laurie T. Krug[1], Robert Yarchoan[1], Joseph Ziegelbauer[1]

*[1]National Cancer Institute, Bethesda, MD, USA*

**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 but can also affect the gastrointestinal tract (GI) in severe cases.

**Methods:** Here, we performed RNA sequencing of skin and GI KS lesions from participants with KS to understand the similarities and differences in the gene

expression pattern. We obtained skin and GI KS lesions with matched normal skin and GI samples. Differential gene expression was measured by comparing KS lesions to normal matched samples. Twenty-two paired samples of KS and normal tissue were obtained (skin (10 pairs) and GI (12 pairs)) from 19 participants with KS,17 participants with concurrent HIV infection. All tumors were stage T1. Seven paired samples were from participants who had received prior KS therapy.

**Results:** In skin KS, cellular gene networks associated with cell adhesion (extracellular matrix), immune response, angiogenesis, and hypoxia were dysregulated when compared with normal skin. There were 25 human genes increased and one decreased in both skin and GI KS lesions. Of these genes, one of particular interest clinically was FLT4, which encodes for a receptor of VEGF-C and VEGF-D. Another gene, STC1, was strongly increased in skin KS lesions, GI KS lesions, and upon laboratory infection of primary endothelial cells with KSHV. We found repression of STC1 and FLT4 inhibited angiogenesis in primary human dermal lymphatic endothelial cells. Infection of these cells with KSHV increased angiogenesis. In participants that shared both skin and GI KS (with matched normal samples), we identified specific genes that were strongly increased in both tissues. Our analysis of KSHV gene expression patterns in KS lesions found abundant expression of certain lytic genes, unexpectedly in the absence of many other lytic genes. KSHV gene expression patterns in KS lesions differed from laboratory infection of endothelial cells with KSHV. Last, KSHV gene expression and IL6 expression strongly correlated in skin KS, but not GI KS lesions.

**Conclusion:** This is one of the first studies comparing skin and GI KS that highlights differences in viral gene and clinically relevant host gene expression between these tissues. This analysis may lead to improved diagnosis and understanding of KSHV pathogenesis.

## 43 ESTIMATING THE LIFETIME RISK OF A DIAGNOSIS OF HIV INFECTION IN THE UNITED STATES

**Sonia Singh**[1], Xiaohong Hu[1], Kristen Hess[1]
[1]*Centers for Disease Control and Prevention, Atlanta, GA, USA*

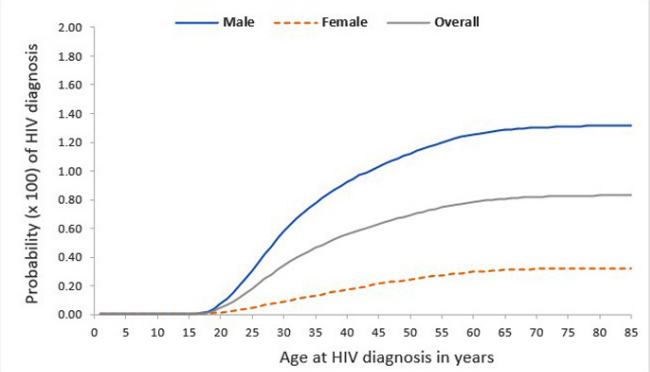
**Background:** Estimates of lifetime risk are used to compare the burden of disease across populations. This method may be a useful tool for clinicians, partners and policy makers when describing the burden of HIV since it can be more readily understood by the public. We estimated lifetime risk of a HIV diagnosis by sex, race/ethnicity and place of residence.

**Methods:** HIV diagnosis, mortality and census population data were used to derive lifetime risk estimates of HIV diagnosis for all ages, by sex, race/ethnicity and place of residence. Data on HIV diagnoses were obtained from the National HIV Surveillance System (NHSS). The numbers of HIV diagnoses (NHSS) and non-HIV deaths (mortality data) during 2017–2019 were used to calculate probabilities of a HIV diagnosis at a given age, conditional on never having received a HIV diagnosis prior to that age using a competing risks method. The lifetime risk estimate is the cumulative probability of HIV diagnosis from birth. The analysis was conducted in DevCan 6.7.3. Comparisons were made to findings from a 2010–2014 analysis.

**Results:** Based on 2017–2019 US data, the lifetime risk of a HIV diagnosis was 1 in 120 overall and 1 in 76 for males and 1 in 309 for females. At every age, males had a higher estimated lifetime risk than females (Figure). Lifetime risk for males was 1 in 27 for Black persons, 1 in 50 for Hispanic/Latino persons, 1 in 89 for Native Hawaiian/other Pacific Islander persons, 1 in 116 for American Indian/Alaska Native persons, 1 in 171 for White persons and 1 in 187 for Asian persons; and for females was 1 in 75 for Black persons, 1 in 287 for Hispanic/Latino persons, 1 in 435 for American Indian/Alaska Native persons, 1 in 611 for Native Hawaiian/other Pacific Islander persons, 1 in 874 for White persons and 1,298 for Asian persons. Lifetime risk improved in all groups except for American Indian/Alaska Native, Hispanic/Latino and Native Hawaiian/other Pacific Islander males and White females, as compared to 2010–2014. By jurisdiction, the lifetime risk ranged from 1 in 39 in DC to 1 in 655 in Wyoming. The states with the highest lifetime risks were Georgia (1 in 59), Florida (1 in 63), Louisiana (1 in 69), Nevada (1 in 84) and Maryland (1 in 85).

**Conclusion:** Overall, lifetime risk of HIV diagnosis has decreased among both males and females, but this decrease was not seen across all races/ethnicities. There is need for continued progress in HIV prevention and treatment since disparities still persist by sex and race/ethnicity.

**Figure. Estimated Lifetime Risk of HIV Diagnosis, by Age and Sex – United States, 2017–2019**




## 44 LARGE HIV CLUSTERS AMONG MEN WHO HAVE SEX WITH MEN IN THE UNITED STATES

**Stephen Perez**[1], Nivedha Panneer[1], Anne Marie France[1], Kathryn Curran[1], Alexandra M. Oster[1]
[1]*Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** Large HIV clusters among people who inject drugs (PWID) have been highly visible. However, the extent to which large clusters occur among other groups has not been described. We described characteristics and growth of large HIV molecular clusters in the United States to guide public health response planning.

**Methods:** We used data reported through March 2021 to characterize clusters first detected during 2018–2019. To detect clusters, we analyzed HIV-1 pol sequences reported to the National HIV Surveillance System for persons with HIV diagnosed in the 3 years prior. We conducted quarterly transmission network analysis, inferring clusters using a pairwise threshold of 0.005 substitutions/site, and identified clusters of rapid transmission (those with ≥ 5 diagnoses during the most recent 12 months). We determined the primary (>50%) risk group (based on transmission category) for each cluster. For large clusters (>25 persons) among men who have sex with men (MSM), we described size at detection and used node ages inferred by molecular clock analysis to estimate HIV transmission rates. We also calculated size and annual growth rate as of March 2021.

**Results:** During 2018–2019, we identified 144 clusters of rapid transmission; 118 (82%) were primarily MSM, 10 (7%) were primarily PWID, and 16 (9%) had no primary risk group. Of 25 large clusters, 17 (68%) were primarily MSM, 6 (24%) were primarily PWID, and 2 (8%) had no primary risk group. Among large MSM clusters, median size at detection was 11; transmission rates at detection ranged from 11–139 transmission events/100 person-years (median: 23/100 py). Large MSM clusters were primarily found in the West (n=8) and the South (n=7), with 2 in the Northeast; 16 of 17 clusters involved >1 state. Median growth rate was 9 persons/year; median size as of March 2021 was 31 persons. Among 528 persons in large MSM clusters, 33% were White, 32% Hispanic/Latino and 26% Black/African American (Table); 4% identified as transgender.

**Conclusion:** Most large, rapidly growing HIV molecular clusters in the United States were primarily MSM. High transmission rates and small cluster sizes at the time of detection, coupled with fast growth rates, indicate that swift response when clusters are first detected has the potential for meaningful public health impact. Demographic data show diversity of race/ethnicity and gender identity among persons in these clusters. Interventions accounting for the unique needs of these networks are needed to halt transmission.

Table. Characteristics of persons in large HIV molecular clusters in the United States, 2018–2019.

| | | Clusters with > 50% MSM (n, col.%) | Clusters with > 50% PWID (n, col%) | Clusters with no risk group >50% (n, col%) |
|---|---|---|---|---|
| Total | | 528 (100) | 371 (100) | 57 (100) |
| Age group at diagnosis | 13–19 years | 50 (9) | 1 (0) | 1 (2) |
| | 20–29 years | 273 (52) | 112 (30) | 21 (37) |
| | 30–39 years | 133 (25) | 157 (42) | 24 (42) |
| | >40 years | 72 (14) | 101 (27) | 11 (19) |
| Race/ethnicity | White | 175 (35) | 290 (78) | 35 (61) |
| | Hispanic/Latino | 170 (32) | 52 (14) | 4 (7) |
| | Black/African American | 137 (26) | 19 (5) | 14 (25) |
| | Other race/ethnicity[1] | 46 (8) | 10 (3) | 4 (8) |
| Risk group | MSM | 406 (77) | 3 (1) | 25 (44) |
| | PWID | 16 (3) | 330 (89) | 13 (23) |
| | Heterosexual persons | 20 (4) | 7 (2) | 8 (14) |
| | MSM who inject drugs | 27 (5) | 20 (5) | 3 (5) |
| | Other/no reported risk | 59 (11) | 11 (3) | 8 (14) |

Abbreviations: MSM, men who have sex with men; PWID, persons who inject drugs
[1] Includes persons reporting American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, or multiple races

## 45 HIV-1 DIAGNOSES IN NORTH CAROLINA, 2018-21: INCIDENT INFECTIONS AND DRUG RESISTANCE

**Shuntai Zhou**[1], Nathan Long[1], Matt Moeser[1], Collin Hill[1], Erika Samoff[2], Victoria Mobley[2], Simon Frost[3], Elizabeth Kelly[1], Scott Shone[2], William Glover[2], Michael Clark[1], Joseph J. Eron[1], Myron S. Cohen[1], Ronald Swanstrom[1], Ann M. Dennis[1]
*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]North Carolina Department of Health and Human Services, Raleigh, NC, USA, [3]University of Cambridge, Cambridge, UK*

**Background:** Knowing the true incidence of HIV-1 infections (recent infections) among people newly diagnosed is pivotal to monitoring the course of the epidemic. We have developed a Primer ID Next Gen Sequencing (PID-NGS) assay to identify recent infection by measuring within-host viral diversity over multiple regions of the HIV-1 genome. We implemented a state-wide project to identify recent infections and transmitted drug resistance mutations (DRMs) in diagnostic samples in near real time.

**Methods:** Serum samples from individuals with newly HIV-1 diagnoses (diagnostic sample collected within 30 days of diagnosis) were sequenced. PID-NGS libraries were constructed covering the coding regions for protease, a portion of reverse transcriptase, integrase, and the env gene. The use of the PID-NGS strategy allows for significant error correction and also a definition of the sampling depth of the viral population. Recent infection was defined as within 9-month of infection. DRMs were summarized at detection sensitivities of 30%, 10% and 1% based on viral population sampling depth.

**Results:** From Jan 2018 to Jun 2021, we successfully sequenced partial genomes from 743 individuals with new diagnoses. Year 2020 had the lowest number of new diagnoses (Fig 1a, red bar). Overall, 39.2% of samples were inferred to have represented infection within the previous 9 months. Percent of recent infection varied significantly over the years, increasing from 29.6% in late 2018 to 50.9% in early 2020, but decreasing significantly to 32.7% in 2021 (Fig 1a, blue lines). Individuals younger than 30 y/o were more likely to be identified with recent infection ($p<0.01$). NNRTI DRMs, especially K103N, were the most abundant DRMs. Fig 1b shows the trend of DRMs over the four years. We observed a trend of decrease in the overall NNRTI DRMs and an increase in the NRTI DRMs in the population. Further analysis suggests that the increase in NRTI DRMs were from TAMs and their revertants, while clinically important NRTI DRMs (K65R and M184) were low (<1%).

**Conclusion:** We have demonstrated a state-wide, all-in-one platform to monitor HIV-1 recency and DRMs in new diagnoses. The number of new diagnoses decreased significantly in 2020 in concert with the COVID-19 pandemic which suggests a decrease in overall HIV testing. The decline in the percentage of recent infections in early 2021 signals a return to broader HIV-1 testing and diagnosis. The increase of other NRTI DRMs suggests ongoing evolution at these sites within the viral population.

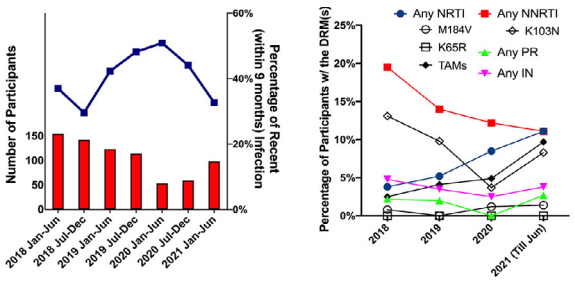



**Fig 1. The change of percent of recent infection among newly diagnosed individuals and transmitted drug resistance mutations (DRMs) in the State of North Carolina from 2018 to June 2021.** a) Number of tested newly diagnosed individuals (red bars) and the percentage of samples inferred to be recent infections (blue lines) from 2018 to 2021. B) Abundance of selected DRMs among newly diagnosed people from 2018 to 2021, using 10% detection sensitivity within the viral population.

## 46 SARS-CoV-2 PREVALENCE IN CHILDREN AND ADULTS IN 15 US COMMUNITIES: THE COMPASS STUDY

**Jessica E. Justman**[1], Timothy M. Skalland[2], Ayana Moore[3], Christopher Amos[4], Mark Marzinke[5], Colleen F. Kelley[6], Rebecca M. Singer[7], Yael Hirsch-Moverman[1], Susanne Doblecki-Lewis[8], David Metzger[9], Elizabeth Barranco[10], Ken Ho[11], Margaret M. Powers-Fletcher[12], Patricia J. Kissinger[13]
*[1]ICAP at Columbia University, New York, NY, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]FHI 360, Durham, NC, USA, [4]Baylor College of Medicine, Houston, TX, USA, [5]The Johns Hopkins University, Baltimore, MD, USA, [6]Emory University, Atlanta, GA, USA, [7]University of Illinois at Chicago, Chicago, IL, USA, [8]University of Miami, Miami, FL, USA, [9]University of Pennsylvania, Philadelphia, PA, USA, [10]Ponce Health Sciences University, Ponce, PR, USA, [11]University of Pittsburgh, Pittsburgh, PA, USA, [12]University of Cincinnati, Cincinnati, OH, USA, [13]Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA*

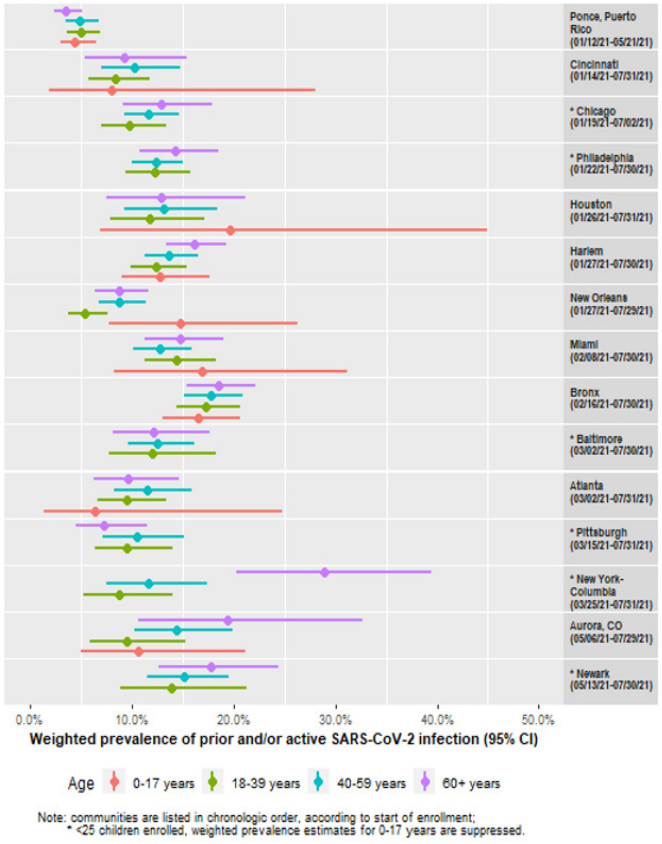
**Background:** There have been few estimates of SARS-CoV-2 seroprevalence in rigorously sampled and geographically broad populations that include children, who have accounted for fewer diagnosed COVID-19 cases compared to adults. The COMPASS study assessed cross-sectional, population-based SARS-CoV-2 seroprevalence and PCR positivity among adults and children in 15 US communities.

**Methods:** Time-location sampling was used to recruit adults and children >2 months of age from randomly selected venues in communities near participating research sites. Demographics, history of COVID-19 and willingness (likely, very likely or already received) to receive an approved COVID-19 vaccine were captured via an interviewer-administered questionnaire. Serologic analysis was performed using a SARS-CoV-2 IgG nucleocapsid antibody (Ab) assay (Abbott Diagnostics, Abbott Park, IL). PCR testing was performed on a mid-turbinate swab using an assay approved by the HPTN Laboratory Center. Prevalence estimates were constructed, overall and by age group (<18 y, 18-39 y, 40-59 y, 60+ y), for each community using survey weights that accounted for the sampling design.

**Results:** A total of 22,732 persons were enrolled (median per community 1,246, range 511 to 2,925) from Jan 2021 to Aug 2021; of these, 2,151 (9.5%) were <18 y. Overall, SARS-CoV-2 seroprevalence (Ab+) ranged from 3.8 to 17.3% (median 12.5%) and SARS-CoV-2 PCR positivity ranged from 0 to 1.9% (median 0.7%). About half of Ab+ and half of PCR+ persons reported no prior or recent (within 14 days) COVID-19 symptoms, respectively [median by community 49.7% (IQR 45.8, 63.9) and 53.6% (IQR 44.3, 58.3)]. Most adults (18+ y) (median 77.3% [69.6 to 92.7%]) reported willingness to get a COVID-19 vaccination; willingness was higher among persons aged 60 y+ [median 88.1%, IQR 83.5, 90.6] compared to those aged 18-39 [median 72.5%, IQR 64.1, 79.8] and 40-59 [median 75.6%, IQR 72.5, 78.4]. The combined prevalence of prior (Ab+) or active (PCR+) SARS-CoV-2 infection across all communities ranged from 4.4 to 17.6% (median 12.7%), and was similar for children (median 12.7%, range 4.4 to 19.7%) and adults (median 12.5%, range 4.4% to 17.8%) among communities enrolling > 25 children (Figure).

**Conclusion:** In this population-based survey, evidence of prior and active SARS-CoV-2 infection varied widely by community but, contrasting with earlier reports, not by age. These findings suggest that acquisition of SARS-CoV-2 is similar across all ages.

Figure: Prevalence of prior or active SARS-CoV-2 infection (Ab+ and/or PCR+)




Note: communities are listed in chronologic order, according to start of enrollment;
* <25 children enrolled, weighted prevalence estimates for 0-17 years are suppressed.

## 47 SAFETY AND EFFECTIVENESS OF THE Ad26.COV2.S VACCINE IN SOUTH AFRICA

**Glenda E. Gray**[1], Nigel Garrett[2], Ameena Goga[3], Lara Fairall[4], Tarylee Reddy[3], Nonhlanhla Yende-Zuma[2], Shirley Collie[5], Ian Sanne[6], Harry Moultrie[7], Fatima Mayat[8], Andrew Boulle[4], Simbarashe Takuva[9], Azwi Takalani[9], Lawrence Corey[9], Linda-Gail Bekker[10]

*[1]South African Medical Research Council, Cape Town, South Africa, [2]Centre for the AIDS Programme of Research in South Africa, Durban, South Africa, [3]South African Medical Research Council, Durban, South Africa, [4]University of Cape Town, Cape Town, South Africa, [5]Discovery, Johannesburg, South Africa, [6]Clinical HIV Research Unit, Johannesburg, South Africa, [7]National Institute for Communicable Diseases, Johannesburg, South Africa, [8]Perinatal HIV Research Unit, Soweto, South Africa, [9]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [10]Desmond Tutu HIV Foundation, Cape Town, South Africa*

**Background:** The Sisonke Phase IIIB open-label implementation study vaccinated health care workers (HCWs) with the single dose Ad26.COV2.S vaccine during two phases of the South African Covid-19 epidemic, dominated first by the Beta followed by the Delta variant of concern.

**Methods:** HCWs were vaccinated over 3 months (17 February - 17 May 2021). Safety was monitored by self-reporting, facility reporting and linkage to national databases. Vaccine effectiveness (VE) against Covid-19 related hospitalisation, hospitalisation requiring critical or intensive care and death, ascertained 28 days or more post vaccination was assessed up until 17 July 2021. Nested sub-cohorts (A and B) from two national medical schemes were evaluated to assess VE using a matched retrospective cohort design.

**Results:** Over the 3-month period, 477234 HCWs were vaccinated in 122 vaccination sites across South Africa. VE derived from the sub-cohorts comprising 215 813 HCWs was 83% (95% CI 75-89) to prevent Covid-19 deaths, 75% (95% CI 69-82) to prevent hospital admissions requiring critical or intensive care and 67% (95% CI 62-71) to prevent Covid-19 related hospitalisations. The VE was maintained in older HCWs and those with comorbidities including HIV infection. VE remained consistent throughout the Beta and Delta dominant phases of the study. 10279 adverse events were reported and 139 (1.4%) were serious, including two cases of thrombosis with thrombocytopenia syndrome and four cases of Guillain-Barré syndrome who recovered.

**Conclusion:** The single dose Ad26.COV2.S was safe and effective against severe Covid-19 disease and death post -vaccination, and against both Beta and Delta variants providing real-world evidence for its use globally.

Table 2: Covid-19 event rates and estimated vaccine effectiveness 28 days after vaccination

| Cohort | Covid-19 hospital admissions | | | Covid-19 related death | | |
|---|---|---|---|---|---|---|
| | Vaccinated | Unvaccinated | VE (95% CI) % | Vaccinated | Unvaccinated | VE (95% CI) % |
| | Events/ P-Y | Events/ P-Y | | Events/ P-Y | Events/ P-Y | |
| Scheme A+B | 302/43770 | 897/43452 | 67 (62,71) | 28/43 802 | 163/43 527 | 83 (75, 89) |
| Scheme A | 153/20128 | 444/19773 | 66 (60,72) | 11/20 145 | 75/19 807 | 85 (75,93) |
| Scheme B | 149/23462 | 453/23679 | 67 (60,73) | 17/23 857 | 88/23 720 | 80 (69, 90) |

P-Y: person years, VE: vaccine effectiveness; *Data on admissions requiring critical/intensive care not available; too few events to analyse deaths.

## 48 COVID-19 BOOSTER VACCINE EFFECTIVENESS IN PEOPLE WITH AND WITHOUT IMMUNE DYSFUNCTION

Late Breaking

**Jing Sun**[1], Qulu Zheng[1], Alfred J. Anzalone[2], Alison G. Abraham[3], Jomol Mathew[4], Nasia Safdar[4], Jessica Y. Islam[5], Amy L. Olex[6], Roslyn B. Mannon[2], Christopher G. Chute[7], Rena Patel[8], Gregory D. Kirk[1]

*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]University of Nebraska Medical Center, Omaha, NE, USA, [3]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [4]University of Wisconsin–Madison, Madison, WI, USA, [5]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA, [6]Virginia Commonwealth University, Richmond, VA, USA, [7]The Johns Hopkins University, Baltimore, MD, USA, [8]University of Washington, Seattle, WA, USA*

**Background:** Real-world evidence on effectiveness of booster or additional doses of COVID-19 vaccine is limited.

**Methods:** Using patient-level data from 50 sites in the U.S. National COVID Cohort Collaborative (N3C), we estimated COVID-19 booster vaccine effectiveness compared to full vaccination alone (completed 2 doses mRNA or 1 dose Janssen vaccine). At each month following full vaccination, we created comparable cohorts of patients with boosters propensity-score matched to those without boosters by age, sex, race/ethnicity, comorbidities, geographic region, prior COVID-19 infection, and calendar month of full vaccination. Booster efficacy was evaluated among patients with and without immunosuppressed / compromised conditions (ISC; HIV infection, solid organ or bone marrow transplant, autoimmune diseases, and cancer). We used Cox regression models to estimate hazards of breakthrough infection (COVID-19 diagnosis after last dose of vaccine) and logistic regression models to compare the risk of death ≤45 days after a breakthrough infection in the boosted vs. matched non-boosted groups.

**Results:** By 11/18/2021, 656390 patients had received full vaccination, and 125409 fully vaccinated had received an additional booster (median time from last vaccine to booster dose: 7.4 months, IQR:6.6, 8.2). At completion of full vaccination, median age was 50 (IQR 33-64) years, 43% male, 50% white, 11% Black, 18% Latinx, 4.8% Asian American/Pacific Islander, and 20% had ISC. People receiving a booster were more likely to be older, male, white, and have ISC. Booster vaccine was significantly associated with a reduced hazard of breakthrough infection (Table). Booster efficacy ranged from 46% (booster receipt 1-4 months after full vaccination) to 83% (receipt 7 months after full vaccination) in people without ISC. Vaccine efficacy was lower, ranging from 43%-65%, in ISC patients (Table). Compared to fully vaccinated patients without booster receipt, patients with booster had an 83% (OR: 0.17, 95% CI: 0.11, 0.28) reduced risk of COVID-19 related death, independent of demographics, geographic region, comorbidities, ISC, prior COVID-19 infection, and time of full vaccination.

**Conclusion:** A booster dose of COVID-19 vaccine has high effectiveness in reducing breakthrough infection risk among all fully vaccinated individuals, though only with moderate effectiveness among ISC patients. Nonetheless, booster vaccination significantly reduced risk for COVID-19 related death regardless of ISC status.

**Table. COVID-19 Booster Vaccine Effectiveness over Time Among Patients with and without Immunosuppression or Immunocompromised Conditions**

| Month since full vaccination | Breakthrough events during follow-up | | Sample size in boosted or non-boosted group* | Hazard Ratio (95% CI) | P-value | Booster vaccine efficacy |
|---|---|---|---|---|---|---|
| | Boosted group | Non-boosted group | | | | |
| **Patients without ISC** | | | | | | |
| ≤4 | 26 | 48 | 1097 | 0.53 (0.33, 0.85) | <0.01 | **45.8%** |
| 5 | <20 | 47 | 902 | 0.25 (0.13, 0.47) | <0.01 | **74.5%** |
| 6 | 26 | 103 | 2753 | 0.25 (0.16, 0.38) | <0.01 | **74.8%** |
| 7 | 94 | 563 | 21925 | 0.16 (0.13, 0.21) | <0.01 | **83.3%** |
| 8 | 289 | 726 | 27660 | 0.39 (0.34, 0.45) | <0.01 | **60.2%** |
| 9 | 201 | 491 | 902 | 0.41 (0.34, 0.48) | <0.01 | **59.1%** |
| **Patients with ISC** | | | | | | |
| ≤4 | 43 | 76 | 1528 | 0.55 (0.38, 0.80) | <0.01 | **43.4%** |
| 5 | 71 | 131 | 2679 | 0.53 (0.40, 0.71) | <0.01 | **45.8%** |
| 6 | 85 | 170 | 4424 | 0.49 (0.38, 0.64) | <0.01 | **50.0%** |
| 7 | 110 | 313 | 10845 | 0.35 (0.28, 0.43) | <0.01 | **64.9%** |
| 8 | 119 | 297 | 12097 | 0.40 (0.32, 0.49) | <0.01 | **59.9%** |
| 9 | 42 | 84 | 5580 | 0.50 (0.34, 0.72) | <0.01 | **50.0%** |

ISC=Immune suppressed or compromised conditions (including people with HIV infection, solid organ or bone marrow transplant, autoimmune diseases, and cancer); 95% CI=95% confidence interval.
*Boosted and non-boosted groups were 1:1 propensity score matched every month after full vaccination by demographics, geographic region, comorbidities, prior COVID-19 infection, and time of full vaccination. Cells with <20 persons were collapsed per N3C requirements.

## 49 INFECTIOUSNESS OF BREAKTHROUGH INFECTIONS AFTER VACCINATION AND NATURAL INFECTION

**Laith J. Abu-Raddad**[1], Hiam Chemaitelly[1]
[1]*Weill Cornell Medicine College in Qatar, Doha, Qatar*

**Background:** SARS-CoV-2 breakthrough infections in vaccinated individuals and in those who had a prior infection have been observed globally, but the transmission potential of these infections is unknown.
**Methods:** Leveraging the national databases, effects of vaccination and of prior infection on SARS-CoV-2 infectiousness were investigated by comparing the RT-qPCR cycle threshold (Ct) values (inversely correlated with viral load and culturable virus) in matched cohorts of primary infections in unvaccinated individuals, reinfections in unvaccinated individuals, BNT162b2 (Pfizer-BioNTech) breakthrough infections, and mRNA-1273 (Moderna) breakthrough infections. Pairwise comparisons were conducted assuming linear and non-linear relationships.
**Results:** Through analyses of the randomly diagnosed infections, the mean Ct value was higher in all cohorts of breakthrough infections compared to the cohort of primary infections in unvaccinated individuals. The Ct value was 1.3 (95% CI: 0.9-1.8) cycles higher for BNT162b2 breakthrough infections, 3.2 (95% CI: 1.8-4.5) cycles higher for mRNA-1273 breakthrough infections, and 4.0 (95% CI: 3.4-4.6) cycles higher for reinfections in unvaccinated individuals. A sensitivity analysis assuming that infectiousness is non-linearly proportional to viral load yielded similar results.
**Conclusion:** Differences imply that breakthrough infections are at least 50% less infectious than primary infections in unvaccinated individuals. Public health benefits of vaccination may have been underestimated, as COVID-19 vaccines not only protect against acquisition of infection, but also appear to protect against transmission of infection.

## 50 COVID-19 VACCINATION RATES IN A GLOBAL HIV COHORT

**Evelynne S. Fulda**[1], Kathleen Fitch[1], Edgar T. Overton[2], Markella V. Zanni[1], Judith A. Aberg[3], Judith S. Currier[4], Michael T. Lu[1], Carlos Malvestutto[5], Carl J. Fichtenbaum[6], Esteban Martinez[7], Triin Umbleja[8], Pamela S. Douglas[9], Heather J. Ribaudo[8], Steven Grinspoon[1]
[1]*Massachusetts General Hospital, Boston, MA, USA,* [2]*University of Alabama at Birmingham, Birmingham, AL, USA,* [3]*Icahn School of Medicine at Mt Sinai, New York, NY, USA,* [4]*University of California Los Angeles, Los Angeles, CA, USA,* [5]*The Ohio State University, Columbus, OH, USA,* [6]*University of Cincinnati, Cincinnati, OH, USA,* [7]*Hospital Clinic of Barcelona, Barcelona, Spain,* [8]*Harvard TH Chan School of Public Health, Boston, MA, USA,* [9]*Duke University School of Medicine, Durham, NC, USA*

**Background:** Little is known regarding global COVID-19 vaccination rates in people with HIV (PWH), a population with significant morbidity from COVID-19. The Randomized Trial to Prevent Vascular Events (REPRIEVE) is a global primary cardiovascular prevention trial among PWH (N=7770) with representation from >100 sites across twelve countries (Brazil, Botswana, Canada, Haiti, India, Peru, Spain, South Africa, Thailand, Uganda, USA, Zimbabwe). Data collected on COVID-19 vaccination rates in REPRIEVE afford a unique opportunity to assess such rates among PWH across global regions.
**Methods:** We assessed cumulative COVID-19 vaccination rates from January through July 2021 among 6952 active participants and compared rates to region- and country-specific vaccination data among the general population, determined from publicly available datasets (CDC, World Bank). Secondarily, within the REPRIEVE cohort, demographic, cardiovascular, and HIV-specific data were compared among those vaccinated vs not via Kaplan-Meier.
**Results:** The cumulative probability of COVID-19 vaccination through the end of July 2021 was 47% among REPRIEVE participants, with rates varying substantially by global burden of disease (GBD) super-region and specific countries. Cumulative vaccination rates (Figure) were highest in the High-Income super-region (64%), followed by Latin America and the Caribbean (51%), Southeast/East Asia (36%), South Asia (16%) and Sub-Saharan Africa (12%). Country-specific rates varied dramatically, with vaccination rates highest in the United States, Peru, and Brazil, 67%, 60%, and 55%, and lowest in South Africa, Uganda, and Haiti with 11%, 3%, and 0%, respectively. Overall factors associated with COVID-19 vaccination among PWH included age, White race, natal male sex, BMI, and higher burden of cardiovascular risk factors, with important differences across GBD super-regions by log-rank test. Vaccination rates among PWH in REPRIEVE were largely comparable to the general population, in most GBD super-regions (Figure), though differences were observed in comparison to the general population in specific countries (data not shown).
**Conclusion:** Global inequities in COVID-19 vaccine access among PWH are apparent, with highest vaccination rates observed among those residing in high-income regions. In addition to region, factors associated with vaccination among PWH included White race, natal male sex, and higher burden of CVD risk factors. Efforts are needed to increase global and regional vaccine rates for PWH.

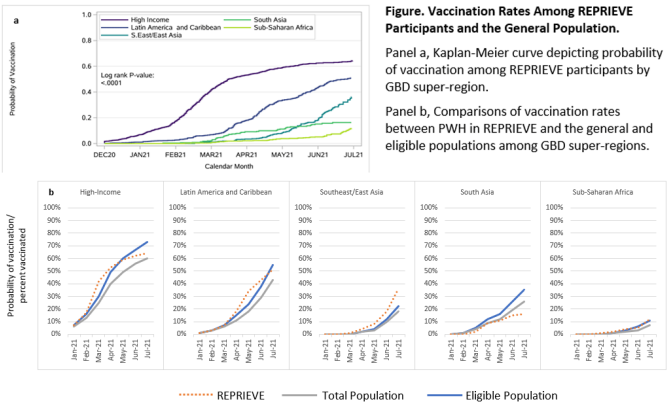



**Figure. Vaccination Rates Among REPRIEVE Participants and the General Population.**

Panel a, Kaplan-Meier curve depicting probability of vaccination among REPRIEVE participants by GBD super-region.

Panel b, Comparisons of vaccination rates between PWH in REPRIEVE and the general and eligible populations among GBD super-regions.

**51 HIV-1 MATURATION - NEW VIEWS OF AN EXTRAORDINARY METAMORPHOSIS**

**John A. Briggs**[1]
[1]*Max Planck Institute of Biochemistry, Martinsried, Germany*

HIV-1 is released from an infected cell in an immature form, before proteolytic cleavage of viral polyproteins by the viral protease triggers rearrangement of the virus into its mature, infectious form. Prior to maturation, the components of the virus are optimised for assembly – they collect all the required components at the assembly site, and release a virus particle into the extracellular space. After maturation the components of the virus are optimised for entry – they bind to and fuse with a target cell, and transport the viral genome to the nucleus to initiate a new round of infection. Proteolytic maturation acts as the switch, flipping the virus from assembly mode into entry mode. Cryo-electron microscopy of individual virus particles, structural biology of virus components, and biochemical and virological data have revealed the structural gymnastics of maturing viral proteins, and the extraordinary, coordinated rearrangement of the virus particle that results. I will review our understanding of HIV-1 maturation with a focus on the structural components of the virus, describe the techniques being applied, and discuss recent data from my lab and other labs.

**52 NEW ROLE FOR INTEGRASE IN VIRAL MATURATION**

**Sebla B. Kutluay**[1]
[1]*Washington University in St Louis, St Louis, MO, USA*

Emerging evidence suggests that the HIV-1 integrase (IN) enzyme plays a critical noncatalytic role in virion maturation, which involves its binding to the viral RNA genome (gRNA) (Kessl et al., Cell 2016). We demonstrated that inhibition of IN-gRNA interactions underlies the pleiotropic effects of numerous class II IN mutations in virus replication (Elliott et al., eLife 2020). In the same study, we showed that IN tetramerization is required for RNA binding and that class II mutations inhibit IN binding to the vRNA through three distinct mechanisms; (i) by decreasing the levels of IN in virions and precluding IN-vRNA interactions, (ii) by impairing IN tetramerization, and (iii) by directly inhibiting IN-vRNA interactions. In addition, we have shown that inhibition of IN-gRNA interactions leads to mislocalization of the gRNA and possibly IN in virions, and their subsequent degradation in target cells (Madison et al., J. Vir. 2017, Elliott et al., eLife 2020), primarily due to lack of protection by the capsid lattice (Eschbach et al., J. Vir. 2020). Building on these key discoveries we continue to decipher the rules of HIV-1 IN-gRNA interactions, how IN-gRNA interactions mediate proper virion maturation and how infected cells sense aberrant particles generated upon inhibition of IN-RNA interactions and capsid destabilization. For example, we have isolated compensatory substitutions in the background of a class II IN (R269A/K273A) variant that directly inhibits IN binding to the gRNA. We found that additional D256N and D270N substitutions in the C-terminal domain (CTD) of IN restored its ability to bind gRNA and led to the formation of infectious particles with correctly matured morphology. Furthermore, reinstating the overall positive electrostatic potential of the CTD through individual D256R or D256K substitutions was sufficient to restore IN-RNA binding and infectivity for the R269A/K273A as well as the R262A/R263A class II IN mutants. As part of the CROI symposium, we will overview these key discoveries and highlight unpublished data demonstrating that electrostatic interactions play a key role in mediating IN binding to the gRNA. Understanding the molecular basis of the second non-catalytic function of IN will not only provide fundamental insight to HIV-1 replication but also help in the development of novel therapies that can complement INSTIs.

**53 STRUCTURE, ASSEMBLY, AND FUNCTIONAL ROLE OF THE INTASOME IN HIV REPLICATION**

**Dmitry Lyumkis**[1]
[1]*Institute for Biological Sciences, La Jolla, CA, USA*

This presentation will discuss the structure, function, composition, and assembly of intasomes. After that, the presenter will examine the relevance of intasomes of antiviral therapies.

**54 SETTING THE STAGE: POSTNATAL PROPHYLAXIS TO REDUCE NEW PEDIATRIC INFECTIONS**

**Claire Thorne**[1]
[1]*University College London, London, UK*

Worldwide, over 1 million infants are born to women living with HIV each year. Postnatal prophylaxis (PNP) for HIV-exposed newborns is a long-established component of intervention packages to prevent vertical transmission, first implemented more than 25 years ago. Today, ART coverage of pregnant women now exceeds 85% globally, with more than half of women already on life-long ART at conception. Higher rates of viral suppression in pregnant and breastfeeding women have contributed to falling vertical transmission rates globally. Whilst late initiation of ART remains a key driver of intrauterine and intrapartum transmissions, the WHO preferred first-line regimen of Dolutegravir plus an NRTI-backbone results in rapid viral load suppression in women starting ART in pregnancy. Given the efficacy of PNP with 2 or 3 drugs in preventing vertical transmission in the scenario of no antenatal ART, enhanced PNP with 2 drugs is recommended by the WHO for "high risk" infants (i.e. those whose mother was diagnosed at delivery or in the postpartum period, who started ART late in pregnancy, was not virally suppressed by delivery or with an incident HIV infection in pregnancy or whilst breastfeeding). However, challenges in implementing enhanced PNP strategies exist, including ascertainment of risk status, whilst there are knowledge gaps around the additional benefit of PNP (standard and enhanced) in the current era. In some resource-rich settings, risk-stratification for PNP has extended beyond the low versus high risk dichotomy, with even shorter (or even no) prophylaxis in infants classified as having very low vertical transmission risk, based on a risk-benefit assessment that includes concerns around toxicity and limiting unnecessary exposure of infants to antiretrovirals. This talk will review the current status of vertical transmission prevention including the roll-out of antenatal ART and the timing of transmission, before examining current PNP guidelines in different settings and related implementation challenges. The place that PNP has in prevention of vertical transmission strategies if all pregnant and breastfeeding women are on ART will be discussed.

**55 ANTIRETROVIRALS FOR PREVENTION: FROM ADULTS TO BABIES**

**Martina Penazzato**[1]
[1]*World Health Organization, Geneva, Switzerland*

Despite decades of progress in decreasing rates of HIV vertical transmission globally, new paediatric infections continue to occur. Postnatal antiretroviral prophylaxis (PNP) remains a critical component of the toolbox available to prevent vertical transmission of HIV. Global guidelines have evolved over the years to better tailor PNP to the changing transmission dynamics influenced by greater coverage for maternal ART, longer duration of breastfeeding as well as persisting delayed ART initiation or suboptimal adherence during pregnancy or breastfeeding. Since 2016 WHO Guidelines have included Enhanced postnatal prophylaxis (ePNP) for infants at increased risk of HIV transmission. While WHO recommendations have been widely adopted, challenges persist with identifying infants at "high risk" and providing ePNP with existing formulations. As a result, countries have adopted a variety of different approaches which may include triple-regimens, longer duration of prophylaxis or simplified approaches without risk-stratification, all resulting in market fragmentation and unreliable supply of commodities. Recent strides made in using novel ARV for pre-exposure Prophylaxis (PreP), have inspired the paediatric HIV community and provided a new impetus to review PNP approaches and explore innovative strategies for the future. Efforts to further reduce the risk of sexually acquired HIV in adults have recently led to the regulatory approval of injectable Cabotegravir extended-release suspension, following the results of 2 randomized controlled trials which demonstrated high efficacy in reducing HIV acquisition risk. In addition, a robust and dynamic pipeline of new antiretrovirals and broadly neutralizing antibodies holds promise for the future of PrEP and provides a compelling rationale to consider some of these agents for postnatal prophylaxis. To date, the scientific community has not identified a validated surrogate for risk of vertical transmission, consequently, very large clinical trials are required to support use of new regimens for PNP. This has prevented the development and introduction of better paediatric prevention regimens since the early investigations of nevirapine in newborns and breastfeeding infants. Overcoming this impasse in PNP innovation will require adaptive study designs or mixed methodologies to study strategies that combine currently approved ARVs for paediatric HIV treatment or consider future agents with novel drug delivery technologies.

**56 SPEED DIALING NEONATES TO THE IDEAL POSTNATAL PROPHYLAXIS REGIMEN**

**Adrie Bekker**[1]
[1]*Stellenbosch University, Cape Town, South Africa*

Among the multitude of antiretroviral drugs (ARVs) licenced today there are few with dosing and safety information available for neonates, and the majority are liquid formulations. Current neonatal ARVs for postnatal prophylaxis (PNP) typically include "older" drugs such as nevirapine and zidovudine, highlighting the need for more potent and safer ARVs in this population. WHO recommends solid ARV formulations for children, but only raltegravir granules are available for use in term neonates. However, this formulation requires multiple steps to administer, is not widely available, and has a low barrier to drug resistance. The time between the first introduction of new ARVs in adults and first data in neonates is often unacceptable. This delay is driven by the lack of pediatric friendly formulations, pharmacokinetic (PK) and safety data. Developmental changes and rapid growth from birth substantially impacts drug disposition, which are even more pronounced in preterm infants. It is difficult to extrapolate drug dosing from young children to neonates due to the immaturity of organs and metabolic enzyme activities in early life. Robust safety monitoring should also be performed as adverse events occur frequently, and reporting is complicated by toxicity grading tables not developed for preterm infants. An additional challenge to conducting PK studies in neonates is the limitation on blood draws owing to small total blood volume. Some of these limitations can be overcome by utilizing infant PK washout samples, sparse PK sampling techniques and application of PK modelling/simulation strategies to inform appropriate dosing. PK efficacy targets in adults are used in children, reducing the need to confirm efficacy in large numbers of neonates. Ongoing and future planned PK studies with solid ARV formulations may provide neonates with better access to effective and solid child-friendly formulations. New long-acting and effective ARVs on the horizon which can be administered intramuscularly or subcutaneously hold out promise for improving PNP options. Broadly neutralizing antibodies (bNAbs) have already been studied in neonates and have been shown to be safe. The combination of long-acting ARVs intravenously and/or subcutaneously administered bNAbs may offer protection against HIV transmission. As a pediatric community we should advocate for access to these newer ARVs to ensure that neonates are not left behind.

**57 PREPARING FOR THE PLATE OF PREVENTION OPTIONS: HOW CAN WE DELIVER?**

**Hyman Scott**[1]
[1]*San Francisco Department of Public Health, San Francisco, CA, USA*

HIV prevention has been revolutionized by biomedical advances in pre-exposure prophylaxis (PrEP) which has changed the trajectory of the HIV epidemic in areas with high uptake. PrEP with daily oral tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) was first shown to be effective for HIV prevention in the iPrEx study more than a decade ago, however despite high effectiveness in subsequent trials, demonstration projects, and clinical studies implementation has been challenged by structural, social, and individual barriers in many jurisdictions. In the US, only 7% of those who may benefit from PrEP have been prescribed PrEP per estimates from the Centers for Disease Control and Prevention. Adherence and persistence remain the "Achilles heel" of daily oral PrEP and new long acting PrEP options, such as bimonthly injections of Cabotegravir long-acting (CAB-LA) which was recently approved by the US Food and Drug Administration in 2021, provides a PrEP option without daily adherence. However, CAB-LA does require adherence to an increased visit schedule and clinical support for administering and tracking injections. New products in development such as Islatravir (as a monthly oral pill or implant), and Lenacapavir (a semi-annual subcutaneous injection) would allow less frequent clinical visits, and potentially require fewer clinical resources. These new PrEP options will provide an important element initially missing from our biomedical toolbox – choice. Using lessons learned from contraception, implementation will need to include low-barrier access such as drop-in and non-traditional hours; an expanded pool of providers to increase service availability; clinician and clinical staff education and training; and policies that help lower out-of-pocket costs for patients. The implementation of these types of strategies will be required to provide an authentic choice of current and burgeoning HIV prevention options.

**58 BUILDING BACK BETTER: PUBLIC HEALTH SYSTEMS, PUBLIC TRUST, AND THE PrEP PIPELINE**

**Kenyon Farrow**[1]
[1]*PrEP4ALL, New York, NY, USA*

The COVID-19 pandemic has helped highlight the long widening gap of trust between the public and biomedical research, health care, and public health systems. Our work to expand current PrEP options and a new pipeline of HIV prevention options for greater uptake will no doubt be challenged in this current environment. This presentation will explore these challenges and offer some potential solutions to restoring the public trust in public health for researchers, providers policymakers, and advocates.

**59 APPLYING LESSONS LEARNED FROM CONTRACEPTION TO PrEP**

**Dominika Seidman**[1]
[1]*University of California San Francisco, San Francisco, CA, USA*

In this presentation, we will discuss lessons learned from the history of contraception, and apply them to PrEP and specifically the use of longer acting PrEP. We will review best practices in offering PrEP methods in a person-centered manner, with the goal of aligning selected methods with the values and preferences of the patient or client. Finally, we will discuss emerging ways to measure and evaluate if PrEP is being offered in person-centered ways, through patient-reported outcomes.

**60 NEW INSIGHTS INTO HIV RNA BIOLOGY**

**Michael Summers**[1]
[1]*University of Maryland, Baltimore County, Baltimore, MD, USA*

HIV-1 RNAs play essential roles in nearly every aspect of viral replication and are targets of synthetic and natural cellular antiviral inhibitors. Over the past decade, studies employing a variety of technological approaches have led to insights into the structural and mechanistic bases for RNA-dependent activities important for viral replication. Molecular determinants of virus restriction were identified in 3D structures of host APOBEC3H and ZAP proteins bound to their HIV-1 RNA targets. Insights into how HIV-1 protects the genome from cellular restriction were derived from studies of the viral capsid and the role it plays in transporting the genome into the nucleus and promoting reverse transcription and integration of the proviral DNA. The discovery that HIV-1 RNAs are transcribed from slightly different start sites revealed how transcripts from a single integrated provirus have distinct functions and fates. Studies further revealed how a single additional G at the 5′ end is sufficient to alter the structure of the viral transcript and modulate exposure of the 5′-Cap, which in turn modulates splicing, translation, and genome packaging. Genomes are packaged as dimers, and there is now considerable evidence that RNA structures adopted by the highly conserved 5′-leader region of the genome control dimerization and packaging. Genomes are selected for packaging by the viral Gag protein, which binds to specific sites on the viral RNA "packaging signal." The MA domain of cytoplasmic Gag recruits cellular tRNAs to promote targeting of Gag:genome complex to assembly sites on the plasma membrane, and Gag-dependent anchoring of the genome to the plasma membrane has been visualized by modern imaging techniques. Genome packaging can be inhibited by molecules that bind to specific sites within the HIV-1 RNA packaging signal, providing important small molecule leads for the development of new RNA-targeting antivirals. Collectively, these and other studies reveal the incredible versatility and myriad functions of viral and cellular RNAs in HIV-1 replication and point to a potential range of strategies for blocking critical functions, augmenting host defenses, or modulating latency.

**61 UNDERSTANDING THE EPIDEMIOLOGY OF COVID-19: A GLOBAL PERSPECTIVE**

**Muge Cevik**[1]
[1]*University of St Andrews, St Andrews, UK*

This keynote talk will provide an overview of the global epidemiology of COVID-19, mainly focusing on disparities in transmission, severity, and outcomes. It will also summarise the challenging and often misinterpreted but consequential epidemiological aspects such as asymptomatic transmission, changes in the severity of disease and transmissibility of variants, and the role of children in transmission dynamics, focusing on better ways to evaluate these areas going forward. The COVID-19 pandemic, with its myriad uncertainties, well-publicised retractions, shifting recommendations and over 300 thousand publications, has

underscored the importance of carefully synthesising and translating the vast amount of data into evidence-based and actionable insights.

## 62 THE IMPACT OF 3BNC117 AND ROMIDEPSIN TREATMENT AT ART INITIATION ON HIV-1 PERSISTENCE

**Jesper D. Gunst**[1], Marie H. Pahus[1], Míriam Rosás-Umbert[1], Thomas Benfield[2], Henrik Nielsen[3], Isik S. Johansen[4], Rajesh Mohey[5], Lars Østergaard[1], Mariane H. Schleimann[1], Martin Tolstrup[1], Julie Fox[6], Michel Nussenzweig[7], Marina Caskey[8], Sarah Fidler[9], Ole Søgaard[1]

*[1]Aarhus University Hospital, Aarhus, Denmark, [2]Hvidovre Hospital, Hvidovre, Denmark, [3]Aalborg University Hospital, Aalborg, Denmark, [4]Odense University Hospital, Odensen, Denmark, [5]Regional Hospital Herning, Herning, Denmark, [6]King's College London, London, UK, [7]Howard Hughes Medical Center, New York, NY, USA, [8]The Rockefeller University, New York, NY, USA, [9]King's College Hospital, London, UK*

**Background:** Interventional reduction of the viral reservoir or induction of HIV-1 remission among individuals on long-term antiretroviral treatment (ART) have largely been unsuccessful. However, studies in non-human primates and mathematical modelling suggest that broadly neutralizing antibodies (bNAbs) or latency reversing agents administration at ART initiation may have a more profound effect on the establishment of HIV-1 latency. Here, we evaluated the impact of the bNAb 3BNC117 and/or latency reversal with romidepsin (RMD) on HIV-1 persistence among individuals starting first-line INSTI-based ART regimens.

**Methods:** In a phase Ib/IIa multicenter controlled trial (the eCLEAR study; NCT03041012), newly diagnosed HIV-1-infected adults were randomized into 1 of 4 groups: a) ART, b) ART+3BNC117 (30 mg/kg) at day 7 and 21 after ART initiation, c) ART+RMD (5 mg/$m_2$) at day 10, 17 and 24, or d) ART+3BNC117+RMD. Participants were followed for 365 days with an optional 12-week analytical treatment interruption (ATI) at day 400. Primary endpoints were time to viral suppression after ART initiation and time to rebound during ATI. Secondary endpoints were safety, changes in cell-associated HIV-1 mRNA and p24 over the interventional period (assessed by flow cytometry). Sensitivity to 3BNC117 was assessed by PhenoSense and HIV env sequencing.

**Results:** Of the 60 enrolled participants, 47% had been infected for less than 6 months. ART effectively suppressed plasma HIV-1 RNA. Compared to ART alone, co-administration of 3BNC117 significantly enhanced the elimination of mRNA+ and p24+ HIV-1-infected CD4 T cells. Phenotypic characterization revealed that this effect was most pronounced in central memory CD4 T cells. Evidence of latency reversal was also observed in both RMD-treated groups. Four of 5 (80%) individuals, whose pre-ART plasma viruses were fully sensitive to 3BNC117, maintained HIV-1 control throughout the ATI compared to 3 of 15 (20%) of the other ATI participants who either had resistant viruses or did not receive 3BNC117 (log-rank, p=0.0248). Most adverse events were mild and unrelated to the study drugs.

**Conclusion:** Co-administration of 3BNC117 at the time of ART initiation among HIV-1-infected individuals reduced the number of productively HIV-1-infected cells. Further, 3BNC117 with or without RMD during ATI initiation may lead to prolonged immunological control during ATI in individuals whose pre-ART viruses are sensitive to the bNAb.

## 63 THERAPEUTIC EFFICACY OF COMBINED ACTIVE AND PASSIVE IMMUNIZATION IN SHIV+ MACAQUES

**Victoria E. Walker-Sperling**[1], Noe B. Mercado[1], Abishek Chandrashekar[1], Erica N. Borducchi[1], Jinyan Liu[1], Joseph P. Nkolola[1], Mark G. Lewis[2], Romas Geleziunas[3], Merlin Robb[4], Nelson L. Michael[4], Maria G. Pau[5], Hanneke Schuitemaker[5], Janet Siliciano[6], Robert Siliciano[6], Dan Barouch[1]

*[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]BIOQUAL, Inc, Rockville, MD, USA, [3]Gilead Sciences, Inc, Foster City, CA, USA, [4]Walter Reed Army Institute of Research, Silver Spring, MD, USA, [5]Janssen Prevention and Vaccines, Leiden, Netherlands, [6]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** The viral latent reservoir is the major barrier to the development of an HIV cure. We previously found that virally suppressed, SIV-infected rhesus macaques treated with the combination of a toll-like receptor 7 (TLR7) agonist and Ad26/MVA vaccination had an increased incidence of virologic control and lower viral loads upon discontinuation of antiretroviral therapy (ART). SHIV-infected macaques treated with TLR7 agonist vesatolimod (VES) and neutralizing Ab PGT121 while on ART also had a lower frequency of and longer time to viral rebound compared to sham. We here treated ART-suppressed, SHIV-SF162P3-infected macaques with Ad26/MVA vaccination, PGT121, and VES, to determine if the combination of the three treatments resulted in outcomes improved from either set of two alone.

**Methods:** Macaques were challenged with SHIV-SF162P3 and initiated ART on day 9 of infection. The animals were sorted into treatment groups as follows: 1) Ad26/MVA vaccination and PGT121 and VES administration (n = 10), 2) Ad26/MVA vaccination and VES administration (n = 12), 3) PGT121 and VES administration (n = 12), or 4) sham treatment. Animals in groups 1-3 were given orally administered VES (0.15 mg/kg) ten times total, once every two weeks from weeks 50-58 and 64-72. Groups 1 and 3 were given five doses of 10 mg/kg PGT121 intravenously once every two weeks, starting at week 64. Groups 1 and 2 were vaccinated intramuscularly with Ad26 vectors at weeks 24 and 36 and boosted with MVA vectors at weeks 48 and 60. ART was discontinued at week 86 of infection to allow for PGT121 wash-out, and animals were followed for an additional 168 days.

**Results:** Upon ART discontinuation, 70% of the animals treated with vaccination, PGT121, and VES either did not rebound or gained virologic control within the follow-up period, compared to 33% in the vaccination and VES group and 42% in the PGT121 and VES group. All three treatment groups had a significantly lower set-point viral load than sham ($p < 0.001$), and the two groups treated with PGT121 had a significantly lower likelihood of rebound ($p < 0.0001$).

**Conclusion:** Our data show that the combination of innate immune stimulation, bNAb administration, and therapeutic vaccination delays rebound and induces immune-mediated virologic control in SHIV-infected macaques upon discontinuation of ART. Using a combination of treatments targeting multiple mechanisms to induce control or prevent rebound is a promising strategy towards establishing a functional cure of HIV-1 infection.

## 64 AZD5582 PLUS SIV mAbs TO REDUCE TISSUE RESERVOIRS IN ART-SUPPRESSED MACAQUES

**Amir Dashti**[1], Sophia Sukkestad[1], Anna M. Horner[1], Margaret A. Neja[1], Nils Schoof[1], Maud Mavigner[1], Jeffrey D. Lifson[2], Shane D. Falcinelli[3], Hannah King[4], Rosemarie D. Mason[4], Richard M. Dunham[3], David M. Margolis[3], Mario R. Roederer[4], Guido Silvestri[5], Ann Chahroudi[1]

*[1]Emory University, Atlanta, GA, USA, [2]AIDS and Cancer Virus Program, Frederick, MD, USA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [5]Yerkes National Primate Research Center, Atlanta, GA, USA*

**Background:** The "shock-and-kill" HIV cure strategy involves latency reversal and immune-mediated clearance of infected cells. Our prior work showed systemic SIV latency reversal using the SMACm / cIAP antagonist AZD5582. Here, we investigated AZD5582 in combination with a cocktail of 4 rhesus-derived SIV Env-specific monoclonal antibodies (mAbs) to reduce viral reservoirs in ART-suppressed rhesus macaques (RMs).

**Methods:** 21 RMs were infected with SIVmac239. ART was initiated 8 wks after infection. After 90 wks of ART, 9 RMs received anti-SIV Env mAbs at 20 mg/kg each s.c. followed by AZD5582 at 0.1 mg/kg i.v. wkly for 5 wks; this cycle was repeated once. 6 RMs received the mAb cocktail only. ART was continued in all RMs until study end. Concentrations of SIV mAbs (ITS09.01-LS, ITS102.01-LS, ITS103.01-LS, ITS113.01-LS specific for V2, CD4bs, CD4bs proximal, and MPER, respectively) were evaluated by ELISA. Latency reversal was monitored by plasma SIV RNA and reservoir size was estimated by qPCR for SIVgag DNA in CD4+ T cells and quantitative virus outgrowth assay.

**Results:** Peak viremia of 107-108 copies/ml occurred 2 wks after SIV infection and ART was successful in suppressing viremia. MAbs peaked in all 15 RMs 24h after infusion with half-lives of 8.6, 6.0, 5.4, and 7.0 days for ITS-09.01-LS, -102.01-LS, -103.01-LS, and -113.01-LS, respectively. AZD5582 led to latency reversal in 7/9 (78%) SIV-infected RMs, with 94/206 (46%) ultrasensitive viral load measurements above baseline. A positive correlation was observed between pre-ART viral load and on-ART viremia during AZD5582 treatment ($r=0.89$, $p=0.002$). Levels of peripheral and lymph node CD4+ T cell-associated SIV-DNA declined over the treatment course. Cross-sectional analysis revealed modestly lower spleen CD4+ T cell-associated SIV-DNA in the AZD5582 + SIV mAbs group compared to controls ($p=0.03$). At study end, virus outgrowth from lymph node CD4+ T cells was significantly lower in the group that received AZD5582 + SIV mAbs compared to controls ($p=0.04$), trended lower in splenic CD4+ T cells, but did not differ in the periphery.

**Conclusion:** Our findings provide insight into a novel HIV cure strategy in a relevant preclinical model and confirm the efficacy of AZD5582 in inducing SIV

reactivation. Importantly, these data suggest that elimination of infected cells in tissues using a cIAP antagonist and Env-targeting mAb cocktail is possible. Optimization of this approach may lead to enhanced reservoir clearance.

65 **HIV-1 REMISSION WITH CCR5Δ32Δ32 HAPLO-CORD TRANSPLANT IN A U.S. WOMAN:IMPAACT P1107**

Late Breaking

**JingMei Hsu**[1], Koen Van Besien[1], Marshall J. Glesby[1], Anne Coletti[2], Savita G. Pahwa[3], Meredith Warshaw[4], Amanda Golner[5], Frederic Bone[5], Nicole Tobin[6], Marcie Riches[7], John W. Mellors[8], Renee Browning[9], Deborah Persaud[10], Yvonne Bryson[6]

*[1]Weill Cornell Medicine, New York, NY, USA, [2]FHI 360, Durham, NC, USA, [3]University of Miami, Miami, FL, USA, [4]Harvard TH Chan School of Public Health, Boston, MA, USA, [5]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [6]University of California Los Angeles, Los Angeles, CA, USA, [7]Center for International Blood and Marrow Transplant Research, Milwaukee, WI, [8]University of Pittsburg School of Medicine, Pittsburgh, PA, USA, [9]National Institute of Allergy and Infectious Diseases, Washington, DC, USA, [10]The Johns Hopkins University School of Medicine, Baltimore, MD, MD*

**Background:** HIV-1 cure has been reported in two men with HIV-1 and malignancy following CCR5Δ32 homozygous allogeneic adult stem cell transplantation. We report on a woman in ART-free HIV-1 remission for 14 months following CCR5Δ32 homozygous cord blood (CB) and CD34-selected haploidentical stem cell transplant (haplo-cord SCT) for acute myeloid leukemia (AML).

**Methods:** IMPAACT P1107 is an observational study of HIV-1 persistence pre- and post- CCR5Δ32/Δ32 CB transplantation for other diseases. Transplant data are from the Center for International Blood and Marrow Transplant Research. Pre- and post-transplant levels of HIV-1 DNA, 2-LTR-circles, and size of the latent replication-competent reservoir (IUPM), plasma viremia (single copy level), HIV-1 antibody, cellular immune phenotypic responses, and HIV-1 tropism were assessed.

**Results:** This middle-aged U.S. woman of mixed race developed high-risk AML while on ART, 4 years after diagnosis of acute HIV-1. She underwent reduced intensity CCR5Δ32/Δ32 haplo-cord SCT and achieved AML remission with a 100% CCR5Δ32/Δ32 CB chimerism by day 100 post-transplant and thereafter. She had early hospital discharge, no acute or chronic GVHD, and asymptomatic CMV and EBV reactivation. Figure 1 shows HIV-1 viral load, antiretroviral treatment, and immune reconstitution profiles. At 37 months post-transplant, she stopped ART (ATI) and has remained aviremic < 1cp/ml for 14 months.

Pre-transplant: HIV-1 DNA (137.4 Gag c/106 PBMC); 2-LTR circles (6.3 c/106 PBMC); plasma HIV RNA (3.3 c/mL); latent reservoir (LR=1.38 IUPM) were all detectable. The proviral pool was CCR5 tropic; she was HIV-1 antibody indeterminate.

Post-transplant: HIV-1 DNA became undetectable (<4.06 c/106 cells), including in CD4+ T cells and bone marrow. Trace levels of 2-LTR circles were transiently detected only at 12 weeks post ATI. LR size was <0.009 IUPM. She is HIV-1 seronegative and has no HIV-1 specific T cell response to Gag. Her engrafted cells show ex-vivo resistance to infection by autologous LR isolates and CCR5/X4 tropic lab strains. No ARVs were detected at multiple timepoints post-ATI.

**Conclusions:** This is the third known case of HIV-1 remission, the first known case in a woman of mixed race, and the first known case with haplo-cord CCR5Δ32/Δ32 SCT. Broader use of CCR5Δ32/Δ32 haplo-cord transplantation should be considered to achieve HIV-1 remission and cure for persons living with HIV-1 requiring SCT for other diseases.

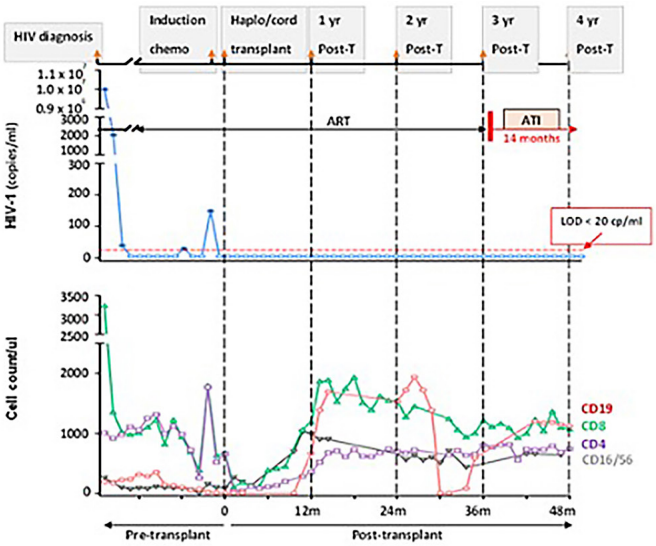



**Figure 1: Top Panel:** Timing of treatment and viral load (measured by a clinical assay with a limit of detection (LOD) <20 copies/mL) profile for HIV-1 and AML in the participant pre and post haplo-cord transplant with CCR5Δ32 /Δ32 cord blood cells. Induction chemotherapy was with idarubicin/ cytarabine; conditioning regimen was fludarabine/melphalan/total body irradiation ($TBI_{600\ cGy}$) with antithymocyte globulin. Post-transplant regimens included: tacrolimus, mycophenolate mofetil for prophylaxis of graft versus host disease (GVHD) for 6 months. Timing of antiretroviral treatment interruption (ATI) relative to transplant is indicated. **Bottom Panel:** Immune reconstitution [T cell subsets ($CD4^+$, $CD8^+$), B ($CD19^+$) and NK ($CD16^+/CD56^+$) cells] post haplo-cord SCT are indicated.

## 66 UNBIASED AND MULTIOMIC ASSESSMENT OF HIV-1–INFECTED CELLS AT SINGLE-CELL RESOLUTION

New Investigator Scholar

**Vincent H. Wu**[1], Son Nguyen[2], Perla Mariana Del Rio Estrada[3], Fernanda Torres-Ruiz[3], Yara A. Luna-Villalobos[3], Santiago Ávila-Ríos[3], Gustavo Reyes-Teran[3], Katharine J. Bar[1], Laura A. Vella[4], Michael Betts[1]
*[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Massachusetts Institute of Technology, Cambridge, MA, USA, [3]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico, [4]Children's Hospital of Philadelphia, Philadelphia, PA, USA*

Background: HIV has no functional cure largely due to the persistent reservoir of latently infected CD4+ T cells containing integrated viral DNA. An understanding of this reservoir is central to targeted elimination strategies, but has been limited by a lack of defining markers and use of models or activation strategies that do not reflect infected CD4+ T cells in vivo. Defining the unmanipulated phenotype of the reservoir requires direct ex vivo approaches to identify targets for cure.

Methods: We performed single-cell Assay for Transposase Accessible Chromatin with Select Antigen Profiling by sequencing (ASAPseq) to identify HIV+ cells using accessible proviral DNA and their coordinate cell surface markers. We tested this strategy with three settings of increasing difficulty: (1) in vitro infection, peripheral blood CD4+ T-cells; (2) chronic infection, lymph node memory CD4+ T-cells; and (3) ART treated, peripheral blood memory CD4+ T-cells. Cells were enriched by bead separation, labeled with oligo-tagged antibodies, and prepared for transposition before single-cell partitioning, library construction and sequencing. Reads were processed using cellranger-atac, AMULET, kallisto, and hiv-haystack for analysis in R (Seurat and ArchR). Viral alignments were made against consensus or autologous sequences.

Results: With the in vitro infection model, we identified 1320 HIV+ cells out of 7069 cells (18.7%) versus 5.1% p24+ cells via flow cytometry. Most HIV+ CD4+ T-cells had an activated/late differentiated phenotype with upregulated markers including CCR5, SLAM, and CD2. There was concordant and significant enrichment of Fos and Jun motifs in open chromatin of HIV+ cells consistent with preferential infection of proliferative and activated cells. In the chronic LNMC, 23 of 3559 cells were HIV+ (0.65%) and were enriched in CD71 and ICOS protein expression, with most being Tfh cells. In on-ART PBMC, we found 36 of 40542 cells were HIV+ (0.09%) largely in late differentiated states, with upregulation of markers including CD2, CCR5, and PD-1.

Conclusion: These findings show that ASAPseq can be used as a direct genomic strategy to identify HIV+ cells ex vivo and define key phenotypes of infected cells. Importantly, ASAPseq does not require stimulation and is done at single-cell resolution, though with limited information on provirus competency. The combined epigenetic and surface antigen profiling of infected cells is a valuable resource for discovery and testing of HIV reservoir elimination strategies.

## 67 EXPANSION AND EXTENSIVE RECIRCULATION OF HIV-INFECTED CELLS IN MULTIPLE ORGANS

New Investigator Scholar

**Caroline Dufour**[1], Maria Julia Ruiz[1], Amélie Pagliuzza[2], Amélie Cattin[1], Tomas Raul Wiche Salinas[1], Syim Salahuddin[3], Stephanie Burke Schinkel[4], Cecilia Theresa Costiniuk[5], Mohammad-Ali Jenabian[3], Petronela Ancuta[1], Jean-Pierre Routy[5], Eric A. Cohen[1], Christopher Power[6], Jonathan B. Angel[4], Nicolas Chomont[2]
*[1]Université de Montréal, Montreal, Canada, [2]Centre de Recherche du CHUM, Montreal, Canada, [3]Université du Québec à Montréal, Montreal, Canada, [4]Ottawa Hospital Research Institute, Ottawa, Canada, [5]McGill University Health Centre, Montreal, Canada, [6]University of Alberta, Edmonton, Canada*

**Background:** Identifying all tissues in which HIV persists during ART is a prerequisite to the design of efficient eradication strategies. Extensive characterization of HIV reservoirs in multiple anatomical sites is only possible by collecting post-mortem tissues within 6 hours following death from people living with HIV who generously gave their body for research on HIV cure.

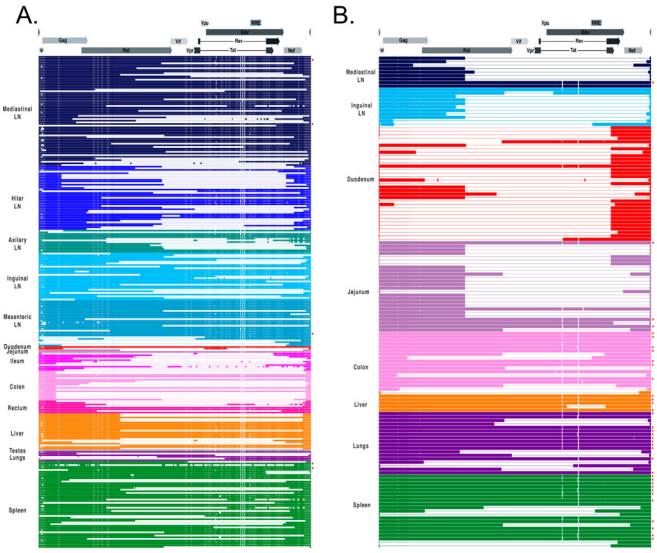
**Methods:** Two men living with HIV (Participant #1 & #2: 67 and 68 years old, on continuous ART for 11 and 8 years; with neuropathy, and non-Hodgkin lymphoma, respectively) underwent rapid deep-tissue sampling after death. HIV DNA and cell-associated gag RNA were quantified by qPCR in snap-frozen tissues (multiple lymph nodes, gut, liver, spleen, brain and testes). Near-full length (NFL) proviral sequences were obtained by a modified FLIPS assay followed by PacBio sequencing.

**Results:** HIV-infected-cells were detected in all tissues examined from both participants. Frequencies of infected cells varied across tissues and between participants, with lymph nodes, liver, lungs and spleen displaying the highest levels of HIV DNA/RNA. A total of 300 (participant #1; 14 tissues) and 141 (participant #2; 8 tissues) NFL genomes were isolated (Figure 1). Participant #2 proviruses often contained large deletions (88% of all defects), whereas viral genomes from participant #1 displayed equally hypermutations (39%) or large deletions (42%). Intact HIV genomes represented 2% and 25% of all proviruses in participants #1 and #2, respectively, and were mainly found in spleen and lymph nodes. In both participants, a large fraction of HIV genomes were found in mutiple copies (49% and 47% in participants #1 and #2, respectively), indicating that clonal expansions are not only common in blood, but also in tissues. The vast majority of these expanded clones were shared accross multiple tissues.

**Conclusion:** This study is the first to report NFL sequencing in multiple deep tissues. Proviral sequencing in samples from these two participants highlights interindividual differences in reservoir integrity and location. Half the viral genomes retrieved from tissues were found to be clonally expanded in both participants, suggesting that persistently infected cells harbouring either intact or defective proviruses expand and recirculate between anatomical sites during long-term ART.

### Fig. 1 Near-full length HIV proviral sequencing in multiple deep-tissues

Alignments of 300 proviruses obtained from 14 tissues from Participant #1 (A) and 141 proviruses obtained from 8 tissues from Participant #2 (B). Each tissue is color-coded. Intact proviruses are indicated by a red asterisk. 100% identical proviral sequences are represented only once.




## 68 SELECTION OF INTACT HIV-1 PROVIRUSES IN DEEP LATENCY DURING LONG-TERM ART

New Investigator Scholar

**Kyra W. Seiger**[1], Xiaodong Lian[1], Elizabeth Parsons[1], Ce Gao1, Gregory T. Gladkov[1], Joshua M. Chevalier[1], Michael M. Lederman[2], Deborah K. McMahon[3], Ronald J. Bosch[4], Jeffrey M. Jacobson[2], Rajesh T. Gandhi[5], Michael J. Peluso[6], Steven G. Deeks[6], Xu Yu[1], Mathias Lichterfeld[1]
*[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Harvard TH Chan School of Public Health, Boston, MA, USA, [5]Massachusetts General Hospital, Boston, MA, USA, [6]University of California San Francisco, San Francisco, CA, USA*

**Background:** Antiretroviral therapy (ART) is highly effective at suppressing HIV-1 replication but does not eliminate infected cells. Host immune responses may influence viral reservoir cell evolution, but such selection effects may only become detectable after prolonged durations of ART. We conducted a high-resolution cross-sectional and longitudinal analysis of the proviral reservoir landscape in long-term ART-treated (LT-ART) patients.

**Methods:** Chromosomal integration sites of intact and defective proviruses were analyzed in people living with HIV (n=8) who had remained on suppressive ART for approximately 20 years, using full-length individual proviral sequencing (FLIP-Seq) and matched integration site and proviral sequencing (MIP-Seq). Corresponding data from individuals with shorter durations of ART (median 9 years) (n=43) were used as a reference cohort.

**Results:** In total, 612 proviral genomes (277 intact, 335 defectives) were obtained; $10_6$ integration sites (64 unique) of intact proviruses and 128 integration sites (85 unique) of defective proviruses were identified. After approximately 20 years of treatment, LT-ART individuals did not show a significant difference in the frequency of total or intact HIV-1 proviruses

compared to individuals with shorter durations of suppressive ART; however, the proportion of clonally-expanded intact proviruses was significantly higher (83% vs 42%, p < 0.0001). Intact proviruses from LT-ART patients showed a highly biased chromosomal integration site profile, with 38%, 23% and 23% of intact genomes being integrated in centromeric/satellite DNA, in non-genic DNA and in ZNF genes, respectively. This represented an apparent contrast to patients with shorter ART duration, in whom 0%, 18% and 13% of intact proviruses were detected in centromeric/satellite DNA, non-genic DNA and ZNF genes, respectively. No difference in chromosomal integration site locations were noted for defective proviruses between the two cohorts. Longitudinal evaluations in n=5 study participants demonstrated a progressive accumulation of intact proviruses in non-genic DNA in LT-ART relative to earlier stages of treatment (15% after 1-2 years ART vs 61% after 17-20 years ART, p=0.002).
**Conclusion:** Long-term ART is associated with progressive enrichment of intact proviruses integrated in repressive heterochromatin locations, likely as a result of immune-mediated selection mechanisms that preferentially eliminate proviruses in more transcriptionally-permissive chromosomal regions.

## 69 SINGLE-CELL MULTIOMICS REVEALS HIV-1 PERSISTENCE IN EXPANDED CYTOTOXIC T-CELL CLONES

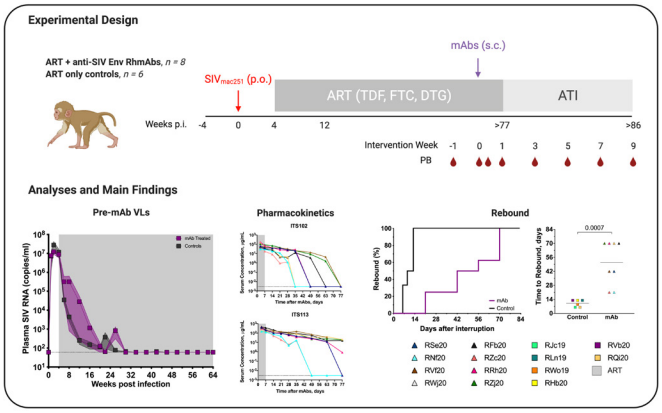
**Jack A. Collora**[1], Runxia Liu[1], Neal Ravindra[1], Delia M. Pinto-Santini[2], Siavash Pasalar[2], Carmela Ganoza[3], Javier R. Lama[3], Ricardo Alfaro[4], Serena S. Spudich[1], Karam Mounzer[5], Pablo Tebas[6], Luis J. Montaner[7], David Van Djik[1], Ann C. Duerr[2], Ya-Chi Ho[1]
*[1]Yale University, New Haven, CT, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Asociación Civil Impacta Salud y Educación, Lima, Peru, [4]Centro de Investigaciones Tecnológicas Biomédicas y Medioambientales, Lima, Peru, [5]Philadelphia FIGHT Community Health Centers, Philadelphia, PA, USA, [6]University of Pennsylvania, Philadelphia, PA, USA, [7]Wistar Institute, Philadelphia, PA, USA*

**Background:** Despite antiretroviral therapy (ART), HIV-1 persists in clonally expanding CD4+ T cells. We hypothesize that HIV-1 persists by residing in T cell clones that proliferate most robustly in vivo. Identifying drivers of the proliferating T cell clones and the HIV-1-infected cells within them may guide strategies that halt the clonal expansion of HIV-1-infected cells.
**Methods:** We obtained paired CD4+ T cells from 6 HIV-1-infected individuals during viremia and after suppressive ART from the Sabes study and from 2 uninfected individuals for comparison. To examine the cellular transcriptional landscape, upstream immune regulators, HIV-1 RNA+ cells, and T cell clonal expansion dynamics, we used single-cell ECCITE-seq to capture surface protein expression, transcriptome, HIV-1 RNA, and T cell receptor (TCR) sequences within the same single cells. We profiled CD4+ T cells and captured the cellular environment of HIV-1 RNA+ cells in their in vivo states without ex vivo stimulations. We next profiled CMV and HIV-1 antigen-specific CD4+ T cells identified by activation induced marker (AIM)(CD69 and CD154) expression after antigen stimulation. We used machine learning algorithms to identify determinants of T cell clone size and HIV-1 RNA+ T cell clones.
**Results:** We captured the single-cell multi-omics landscape of 215,458 CD4+ T cells (267 HIV-1 RNA+ cells and 68 expanded HIV-1 RNA+ T cell clones) from 6 HIV-1-infected individuals and 2 uninfected individuals. We found that despite ART, antigen and TNF responses persisted and shaped T cell clonal expansion. HIV-1 RNA+ cells persisted in larger T cell clones both during viremia and after viral suppression. HIV-1 resided in Th1 polarized, HIV-1 and CMV-responding T cells expressing Bcl-2 family anti-apoptotic genes. Although HIV-1 RNA+ cells were heterogeneous, HIV-1 RNA+ T cell clones were enriched in cytotoxic T effector memory Th1 cells. Using flow cytometry, we found that HIV-1 p24+ cells were enriched in granzyme B+ effector memory T cells from both the Sabes study (Lama et al. CID 2021) and an independent cohort from the Wistar Institute.
**Conclusion:** HIV-1 RNA+ T cell clones are larger in clone size, established during viremia, persistent after viral suppression, and enriched in GZMB+ cytotoxic effector memory Th1 cells which are not exclusively responsive to HIV-1 or CMV antigens. Targeting HIV-1-infected cytotoxic CD4+ T cells and drivers of clonal expansion provides a new direction for HIV-1 eradication.

## 70 DELAYED VIRAL REBOUND FOLLOWING ANTIBODY ADMINISTRATION IN INFANT MACAQUES

**Jenna S. Powers**[1], Katherine M. Bricker[1], Brianna Williams[1], Danielle Oliver[1], Veronica Obregon-Perko[1], Dormarie E. Rivera Rodriguez[1], Sophia Sukkestad[1], Amir Dashti[1], Rosemarie D. Mason[2], Mario R. Roederer[2], Ann Chahroudi[1]
*[1]Emory University, Atlanta, GA, USA, [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

**Background:** Antiretroviral therapy (ART) does not eliminate the latent HIV reservoir. Interventions to prevent viral rebound in the absence of ART would be highly beneficial for the 1.7 million children living with HIV. Treatment with bNAbs demonstrated a delay in time to rebound in adult clinical trials but have not yet been evaluated in a pediatric clinical or preclinical study that includes analytical treatment interruption (ATI).
**Methods:** Env-specific mAbs were isolated from SIV-infected RMs and expressed as full-length rhesus IgG1 modified to contain the LS-encoding mutation (M428L/N434S) to maximize circulation half-life. We evaluated the impact of 4 anti-SIV Env RhmAbs: ITS09.01-LS, ITS102.01-LS, ITS103.01-LS, ITS113.01-LS (anti-V2, CD4BS, CD4BS proximal, and MPER, respectively), selected for ability to neutralize SIVmac251. Fourteen rhesus macaque (RM) infants were orally challenged with SIVmac251 at 4 wks of age and treated with a triple ART regimen (TDF+FTC+DTG) for ~16 months beginning 4 wks post infection. Eight RMs received a s.c. injection at 20 mg/kg of each anti-SIV Env RhmAb one wk prior to ATI and six RMs remained on ART alone until ATI. Time to viral rebound and post rebound set point were monitored by quantitative PCR for SIVgag RNA in plasma. Serum RhmAb concentrations were measured by ELISA.
**Results:** All infant RMs were infected with peak viral loads of $10_6$ -$10_8$. ART was successful in suppressing viremia to <60 copies/ml in all RMs with few blips. Treatment with RhmAbs was safe in our pediatric model, with no adverse clinical events. All infant RMs rebounded after ART interruption; however RhmAb-treated RMs experienced a significant delay in time to rebound compared to ART only controls (p = 0.0007; mean = 51d vs 10d, respectively). A positive correlation was observed between the time to rebound following ATI and the duration of detectable ITS113.01-LS in serum (r=0.78, p=0.04) as well as a positive trend for the time to rebound and mAb concentration during ATI. Of the 8 RhmAb-treated RMs, the two that exhibited the shortest time to rebound following ATI had the most rapid decline in serum RhmAb concentration.
**Conclusion:** In summary, we have demonstrated that a single administration of an anti-SIV Env RhmAb cocktail prior to ATI leads to delayed time to rebound in infant RMs. This research provides preclinical support for the use of polyfunctional mAbs to delay viral rebound in pediatric HIV-1 cure clinical trials.




## 71 NOVEL qPCR APPROACH REVEALS DYNAMICS OF HBsAg DERIVED FROM INTEGRATED HBV (iDNA)

**Tanner Grudda**[1], Hyon S. Hwang[1], Mark S. Sulkowski[1], Maraake Taddese[1], Richard Sterling[2], Ashwin Balagopal[1], Chloe L. Thio[1]
*[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Virginia Commonwealth University, Richmond, VA, USA*

**Background:** Functional hepatitis B virus (HBV) cure is loss of circulating hepatitis B surface antigen (HBsAg). With current anti-HBV therapy, HBsAg usually persists, but it is unknown whether the source is either covalently closed circular DNA (cccDNA), iDNA, or both. To address this, we developed a novel approach using qPCR assays to discriminate iDNA-derived from cccDNA-derived

surface transcripts (S) on 7 paired liver tissues from HIV/HBV co-infected participants in a Hepatitis B Research Network ancillary study.

**Methods:** Our approach uses 3 distinct primer/probe pairs of comparable efficiency that target (A) 5' end of pre-genomic RNA, (B) all S and longer transcripts, and (C) common 3' end of all cccDNA-derived transcripts. iDNA yields truncated S transcripts that lack the viral downstream target (C). Quantities yielded by these assays were used to determine the relative amounts of iDNA-compared to cccDNA-derived S by estimating the amount of S transcripts that lacked common 3' ends in RNA extracts from 7 paired liver tissues (5 HBeAg+/2 HBeAg-). Biopsies were separated by 3-4 years on HBV-active antiretroviral therapy (ART). Total (unfractionated) quantitative HBsAg (qHBsAg) was measured by ELISA in contemporaneous serum samples.

**Results:** Five individuals (3 HBeAg+, 2 HBeAg-) had <1 $log_{10}$ decline in serum qHBsAg (range: 0.08–0.44 IU/mL) while two (HBeAg+) had ≥1 $log_{10}$ declines. At biopsy 1, S derived more from iDNA than from cccDNA in both HBeAg-individuals (12- and 71-fold more), and after 3.5 and 3.7 years of ART, the iDNA-derived S became more dominant compared to cccDNA-derived S (185- and 222 –fold more). Similarly, in HBeAg+ persons with <1 $log_{10}$ decline in qHBsAg, the amount of iDNA- compared to cccDNA-derived S transcripts increased from biopsy 1 (0.73-, 1.2-, 4.3-fold more) to biopsy 2 (0.95-, 27-, 55-fold more) increased. In contrast, the two HBeAg+ individuals with ≥1 $log_{10}$ declines in qHBsAg had commensurate amounts and declines in iDNA- and cccDNA-derived S during ART (Figure).

**Conclusion:** Using a novel multi-PCR platform, we discovered that HIV/HBV co-infected persons with >1 $log_{10}$ declines in qHBsAg during ART had primarily cccDNA-derived S, whereas persons with minimal qHBsAg changes had mostly iDNA-derived S that enriched with time. These data suggest that further work is required to determine if hepatocytes with iDNA need to be eliminated and if tailored therapeutic approaches are needed for an HBV functional cure.

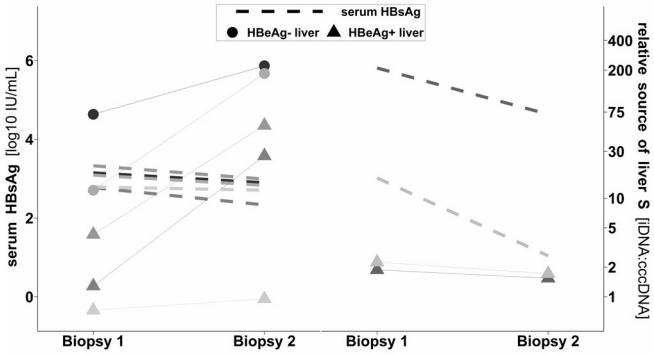



*Figure. We quantified serum HBsAg levels and iDNA- and cccDNA-derived S in bulk liver in 7 people at two time points separated by 3-4 years on HBV-active ART. Persons with <1 log10 IU/mL declines in serum HBsAg had S transcription predominantly from iDNA(left), whereas persons with ≥1 log10 IU/mL decline had S transcription chiefly from cccDNA (right). Symbols are the iDNA:cccDNA at each liver biopsy for each person. Dotted lines are changes in serum HBsAg.*

## 72 MODELING IMPACT OF THE COVID-19 PANDEMIC ON HEPATITIS C VIRUS ELIMINATION IN THE US

**Ricardo E. Flores Ortega**[1], Martin Hoenigl[1], Jaskaran S. Cheema[1], Nancy Reau[2], Natasha Martin[1]

*[1]University of California San Diego, La Jolla, CA, USA, [2]Rush University Medical Center, Chicago, IL, USA*

**Background:** Due to the COVID-19 pandemic, hepatitis C virus (HCV) treatment in the U.S. reduced by 30% in March 2020 and remained low throughout the end of 2020, but the impact on HCV elimination is unknown. We use modeling to estimate the impact of the COVID-19 pandemic on the likelihood of reaching the World Health Organization (WHO) and U.S. National Academies of Sciences and Engineering (NASEM) HCV elimination targets by 2030 (80% reduction in HCV incidence, 65% reduction in HCV mortality from a 2015 baseline).

**Methods:** We developed a general population model that simulates HCV transmission and progression in the U.S. The model is stratified by age and risk (young adult (20-30 years) non PWID, young adult (20-30 years) PWID, adults (31-51 years), and older adults (≥ 52 years)), HCV disease stage, diagnosis, and treatment status. The model was calibrated to data from the literature on number of chronic infections in 2011 and 2018, number aware of their infection and number cured in 2018. The model was validated against U.S. Centers for Diseases Control estimates of new HCV infections in 2019. We used the calibrated model to simulate the impact on HCV incidence and HCV-related mortality from 2015-2030 with: (1) no disruption to treatment uptake from 2020 onwards; (2) 1-year reduction in treatment (by 30%) from 2020 (as observed in national data), and (3) 2-year reduction in treatment (by 30%) followed by return to status quo.

**Results:** We estimated there were 67,267 (95%CI 23,433-114,471) new HCV infections in 2015. Under all scenarios the 80% incidence reduction target is missed (29.7% reduction by 2030 even with no disruption to treatment, even less impact with COVID disruptions). There are overall 990 (95% 417-1,330) additional new infections from 2015-2030 for the 1 year disruption, and 1,933 (95% 800-2,599) additional new infections for the 2 year disruption. Similarly, all projections fail to meet the mortality target by 2030, with an anticipated relative reduction in mortality of 30.6% (95% 21.7-38.4%) with a 1 year disruption.

**Conclusion:** The U.S. was not on track to achieve the WHO and U.S. NASEM elimination targets pre-pandemic and has fallen further behind during the COVID-19 pandemic. Urgent scale-up of HCV diagnosis, treatment, and prevention is required.

## 73 EFFECT OF DIRECT-ACTING ANTIVIRALS ON HCV INCIDENCE AMONG PEOPLE LIVING WITH HIV

**Daniela K. Van Santen**[1], Rachel Sacks-Davis[1], Marc Van der Valk[2], Mark Stoove[1], Andri Rauch[3], Inma Jarrín[4], Karine Lacombe[5], Linda Wittkop[6], Gail Matthews[7], Joseph Doyle[1], Marina B. Klein[8], Maria Prins[9], Tim Spelman[1], Margaret Hellard[1]

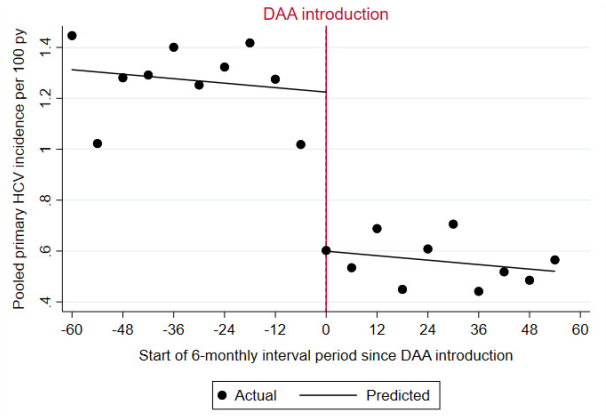
*[1]Burnet Institute, Melbourne, Australia, [2]Academic Medical Center, Amsterdam, Netherlands, [3]University Hospital Bern, Bern, Switzerland, [4]Instituto de Salud Carlos III, Madrid, Spain, [5]Sorbonne University, Paris, France, [6]University of Bordeaux, Bordeaux, France, [7]Kirby Institute, Sydney, Australia, [8]McGill University Health Centre, Montreal, Canada, [9]Public Health Service Amsterdam, Amsterdam, Netherlands*

**Background:** The World Health Organization (WHO) strategy to eliminate hepatitis C virus (HCV) as a public health threat aims at reducing incidence by 30% in 2020 and by 80% in 2030 compared to 2015. Universal access to direct-acting antivirals (DAA) can reduce HCV incidence through a treatment as prevention effect. We aim to monitor progress towards HCV elimination, including changes in primary HCV incidence by calendar year and following DAA introduction among people living with HIV (PLHIV).

**Methods:** We used pooled data from 6 cohorts from the International Collaboration on Hepatitis C Elimination in HIV-coinfection (InCHEHC), including data from the Netherlands, Switzerland, Australia, Spain, and France (2010-2019). For incidence, follow up started from the first negative HCV-antibody test date until last negative antibody test or infection date which was estimated as the midpoint between last negative and first positive test dates. To monitor elimination progress, we calculated annual rates. We used interrupted time series analysis to assess the effect of DAA introduction on incidence. We aggregated data in 6-monthly intervals. Time zero was aligned across cohort to indicate the interval between the date of DAA introduction in each country to 6 months thereafter.

**Results:** Of 86,250 participants, 45,933 had at least one HCV antibody negative result and a subsequent test. During 248,186 person-years (py), we observed 2,051 incident infections. Incidence decreased from 0.91 per 100 py (95%CI=0.80,1.03) in 2015 to 0.46 per 100 py (95%CI=0.35,0.60) in 2019, reflecting a 49% decrease. Mean incidence in the pre-DAA period was 1.27 per 100 py. Interrupted time-series analysis estimated that pre-DAA incidence was declining slowly by 0.009 per 100 py (95%CI=-0.05,0.04) per 6-month interval (Figure). In the first 6 months following DAA introduction, a 51% (absolute change=-0.62 95%CI=-0.90,-0.35) drop in incidence was observed. Mean incidence in the DAA period was 0.56 per 100 py. Post-DAA incidence continued to decrease by 0.009 per 100 py (95%CI=-0.02,-0.005) per 6-month interval.

**Conclusion:** Our data suggests the countries from which our cohorts are drawn are on track to meet the WHO elimination incidence target for PLHIV in care by 2030. A rapid decline in primary HCV incidence was observed shortly following DAA introduction and incidence remained low, with a slow ongoing decline thereafter. Our findings indicate that greater efforts and new strategies are needed to achieve further incidence reductions.




## 74 VORICONAZOLE OR AMPHOTERICIN B DEOXYCHOLATE: WHICH IS THE PREFERRED INDUCTION THERAPY

**Yihong Zhou**[1], Yuanyuan Qin[1], Yanqiu Lu[1], Jing Yuan[1], Jingmin Nie[1], Min Liu[1], Qun Tian[2], Ke Lan[3], Guoqiang Zhou[4], Yingmei Qin[5], Kaiyin He[6], Jianhua Yu[7], Jun Liu[8], Vijay Harypursat[1], Yaokai Chen[1]

*[1]Chongqing Public Health Medical Center, Chongqing, China, [2]The Third People's Hospital of Guilin, Guangxi, China, [3]Longtan Hospital of Guangxi Zhuang Autonomous Region, Guangxi, China, [4]The First Hospital of Changsha, Hunan, China, [5]The Fourth People's Hospital of Nanning, Guangxi, China, [6]Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangdong, China, [7]Xixi Hospital of Hangzhou, Zhejiang, China, [8]Kunming Third People's Hospital, Yunnan, China*

**Background:** Even in the era of widespread ART, HIV-associated talaromycosis is still common in endemic areas globally. Current guidelines recommend liposomal amphotericin B as the preferred induction therapy, but liposomal amphotericin B is not available in certain settings. Induction therapy with amphotericin B deoxycholate or voriconazole has been shown to be effective treatments for talaromycosis. However, prospective clinical trials comparing these two drugs are absent from the literature

**Methods:** In this open-labelled, multicenter, prospective controlled trial, we enrolled patients at 17 hospitals in China from 2019 to 2020. A total of 359 patients received treatment with either intravenous amphotericin B deoxycholate or voriconazole. Each individual was invited to participate in a 48-week follow-up. The primary end point was all-cause mortality during the first 2 weeks after baseline. Secondary end points were mortality at week 48, clinical resolution of talaromycosis, fungal clearance at week 2, and the development of the immune reconstitution inflammatory syndrome (IRIS).

**Results:** We observed no difference in the risk of death at weeks 2 or at week 48 after multivariable logistic regression and multivariable Cox proportional-hazards modelling. Logistic regression analysis revealed a significantly lower odds ratio of clinical resolution (aOR=0.543, 95% CI: 0.338-0.872) and fungal clearance (aOR= 0.605, 95% CI: 0.377-0.972) over the course of 2 weeks in voriconazole users than in amphotericin B deoxycholate users. A higher number of patients in the amphotericin B deoxycholate group than in the voriconazole group had hemoglobin levels <74 g/L (p=0.015) and potassium levels <2.4 mmol/liter (p=0.009).

**Conclusion:** Induction therapy using voriconazole had a similar efficacy in terms of all-cause mortality rate to induction therapy using amphotericin B deoxycholate in HIV-infected patients with talaromycosis over a 48-week observation period. Amphotericin B deoxycholate contributed to earlier fungal clearance and clinical resolution of symptoms, but was more likely to develop myelosuppression and hypokalemia. In contrast, voriconazole had fewer adverse effects than amphotericin B deoxycholate, but seemed less effective in clinical resolution and fungal clearance.

## 75 CLUSTER RCT OF A MID-LEVEL MANAGER INTERVENTION TO PROMOTE IPT UPTAKE IN UGANDA

**Elijah Kakande**[1], Canice Christian[2], Laura B. Balzer[3], Joshua R. Nugent[3], William Dileso[2], Derek Rast[2], Jane Kabami[1], Jason Johnson Peretz[2], Carol S. Camlin[2], Starley R. Shade[2], Elvin H. Geng[4], Dalsone Kwarisiima[1], Moses R. Kamya[1], Diane V. Havlir[2], Gabriel Chamie[2]

*[1]Infectious Diseases Research Collaboration, Kampala, Uganda, [2]University of California San Francisco, San Francisco, CA, USA, [3]University of Massachusetts Amherst, Amherst, MA, USA, [4]Washington University in St Louis, St Louis, MO, USA*

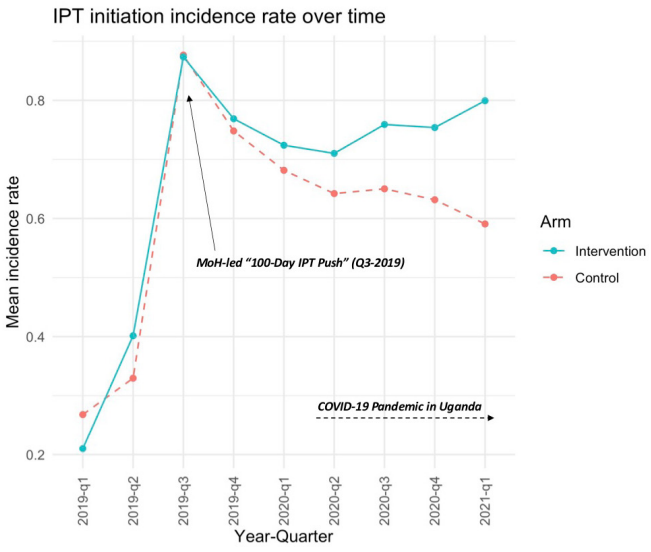
**Background:** Despite longstanding guidelines endorsing isoniazid preventive therapy (IPT) for persons with HIV, uptake is low across sub-Saharan Africa. Mid-level health managers oversee IPT programs nationally; interventions aimed at this group have not been tested.

**Methods:** We conducted a cluster randomized trial in Uganda among district-level health managers from 2017-2021. The unit of randomization was groups of 4-7 managers. Our intervention convened managers into mini-collaboratives facilitated by Ugandan TB/HIV experts and provided business leadership/management training, SMS platform access, and data feedback. The primary outcome was IPT initiation rates among adults with HIV in health facilities overseen by participants over 2 years (2019-2021). We compared incidence rates using cluster-level targeted minimum loss-based estimation. We conducted pre-specified analyses that excluded Q3-2019 to understand intervention effects independent of a national "100-day push" of IPT tied to a financial contingency during Q3-2019. Qualitative interviews were analyzed to ascertain mechanisms of intervention action.

**Results:** Managers from 82/82 eligible districts (61% of Uganda's 135 districts) were enrolled and randomized: 43 districts to intervention, 39 to control. After one year, in 5-point-Likert quantitative surveys, intervention-group managers demonstrated greater increases in familiarity with IPT (by +0.47 points (95%CI:0.14-0.80)) and knowledge of IPT efficacy (+0.59 points (95%CI:0.06-1.12)) as compared to control. Intervention-group managers reported improved within-district communication and inter-district collaboration and feeling empowered to better manage frontline providers, in contrast to control, in qualitative interviews. Over two years, the IPT initiation rate was 0.74 vs. 0.65 starts/person-year in intervention vs control: incidence rate ratio (IRR)=1.14 (95%CI:0.88-1.46; p=0.16). Excluding Q3-2019, IPT initiation was higher in intervention vs control: 0.32 vs. 0.25 starts/person-year (IRR=1.27, 95%CI:1.00-1.61, p=0.03; Figure).

**Conclusion:** Though overall IPT initiation rates were not significantly higher with the mid-level manager intervention in this cluster randomized trial, rates were significantly higher compared to control when excluding the massive MoH-led "100-day IPT push" in both arms. The higher rates were sustained during the COVID-19 pandemic, suggesting benefits of targeted leadership and management training for mid-level health managers.

**Figure:** IPT initiation incidence rates over time in intervention (solid line) vs. control (dashed line) arms of a cluster randomized trial of a mid-level health manager intervention to promote IPT uptake in Uganda.



## 76 RANDOMIZED CONTROLLED TRIAL OF ADJUNCTIVE ROSUVASTATIN FOR TUBERCULOSIS TREATMENT

**Gail B. Cross**[1], Intan Permata Sari[1], Cissy Kityo[2], Yogesh Pokharkar[3], Han-Nguyen Thi[4], Quyet Do[4], Emmanuel Gutierrez[5], Victoria Dalay[5], Vincent M. Jr[6], Henry Mugerwa[7], Ka-Lip Chew[8], Nicholas Paton[1]

*[1]National University of Singapore, Singapore, Singapore, [2]Joint Clinical Research Centre, Lubowa, Uganda, [3]Singapore Clinical Research Institute, Singapore, Singapore, [4]Vietnam Military Medical University, Ha Noi, Viet Nam, [5]De La Salle Medical and Health Sciences Institute, Cavite, Philippines, [6]Lung Centre of the Philippines, Quezon City, Philippines, [7]Joint Clinical Research Centre, Kampala, Uganda, [8]National University Health System, Singapore, Singapore*

**Background:** In vitro and animal model data suggest statins may have benefit as adjunctive host-directed therapy for tuberculosis. Rosuvastatin has minimal interaction with rifampicin and is available in generic formulation. We hypothesised that rosuvastatin, at standard treatment doses used for lipid reduction, might accelerate sputum culture conversion.

**Methods:** We randomised patients with rifampicin-susceptible TB (smear ≥1 positive and/or quantitative GeneXpert ≥ medium) to receive rosuvastatin (10mg daily for 8 weeks; optional 5mg lead in for 2weeks) in addition to standard treatment (rifampicin, isoniazid, pyrazinamide, ethambutol for 8 weeks, then rifampicin and pyrazinamide for 16 weeks) [rosuvastatin group] or standard treatment alone [control group]. We collected weekly sputum samples for culture in liquid (mycobacteria growth indicator tube) and solid media. The primary efficacy endpoint was time to culture conversion (TTCC) measured in liquid culture within 8 weeks from randomisation; TTCC in solid culture was a secondary endpoint; the co-primary safety endpoint was incident grade 3/4 adverse events by 24 weeks. TTCC was compared between rosuvastatin and control groups using Cox proportional hazards regression model; the trial had 80% power to detect an effect size (hazard ratio, HR) of 1.8 on TTCC.

**Results:** Of the 137 patients randomised, 135 were included in the modified intention to treat analysis population (68 rosuvastatin, 67 control; 59% Uganda, 25% Vietnam, 16% Philippines; 25% female; 4% HIV co-infected). Median TTCC (liquid) was 42 (95%CI 35-49) days in the rosuvastatin group and 42 (36-53) days in the control group; HR 1.30, 95%CI 0.88-1.91; P=0.188. HR appeared to be higher HR in Asian vs African patients, but there was no difference in other pre-specified subgroups (Table 1). Median TTCC (solid) was 28 (21-35) days in the rosuvastatin group and 35 (28-36) days in the control group; HR 1.36, 0.95-1.94; P=0.091. Grade 3/4 adverse events occurred in 5 patients in the rosuvastatin group (none leading to rosuvastatin discontinuation) and 4 patients in the control group.

**Conclusion:** Rosuvastatin was well tolerated but the effect size was modest, without statistical evidence of benefit on liquid culture conversion and with weak evidence of benefit on solid culture conversion. The difference in effect size between ethnic subgroups may reflect differences in drug exposure and suggests that further trials exploring population or patient-adjusted higher doses may be of value.

Table 1: TTCC in MGIT (liquid culture), pre-specified subgroup analyses

| Subgroup, (number in subgroup) | | Rosuvastatin Median days (95%CI) | Control Median days (95%CI) | HR (95% CI) | P |
|---|---|---|---|---|---|
| Ethnicity | Asian (55) | 36.0 (28.0, 49.0) | 42.0 (36.0, 49.0) | 1.65 (0.90, 3.05) | 0.107 |
| | African (80) | 42.0 (35.0, 49.0) | 42.0 (35.0, 56.0) | 1.08 (0.65, 1.78) | 0.768 |
| CXR cavitation at baseline | Yes (106) | 42.0 (35.0, 49.0) | 42.5 (36.0, 56.0) | 1.24 (0.80, 1.92) | 0.330 |
| | No (29) | 38.5 (32.0, 42.0) | 42.0 (28.0, - ) | 1.33 (0.56, 3.14) | 0.518 |
| Smear status at baseline | ≥ 2+ (58) | 49.0 (42.0, 52.0) | 56.0 (35.0, 56.0) | 1.29 (0.69, 2.44) | 0.427 |
| | < 2+ (75) | 35.0 (28.0, 42.0) | 42.0 (36.0, 45.0) | 1.25 (0.77, 2.04) | 0.365 |

## 77 PK OF DOSE-ADJUSTED EMERGENCY CONTRACEPTION WITH RIFAMPICIN THERAPY IN ACTG A5375

**Rosie Mngqibisa**[1], Laura M. Smeaton[2], Maxine Olefsky[2], Anthony T. Podany[3], Elizabeth Barr[4], Pablo Belaunzaran[5], Sharlaa Badal-Faesen[6], Evans Kachale[7], Cecelia Kanyama[8], Marije Van Schalkwyk[9], Elizabeth Woolley[10], Susan E. Cohn[11], Catherine Godfrey[12], Kimberly K. Scarsi[13]

*[1]Enhancing Care Foundation, Durban, South Africa, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University of Nebraska Medical Center, Omaha, NE, USA, [4]Office of Research on Women's Health, Bethesda, MD, USA, [5]National Institute of Allergy and Infectious Diseases Division of AIDS, Bethesda, MD, USA, [6]University of the Witwatersrand, Johannesburg, South Africa, [7]Johns Hopkins Research Project, Blantyre, Malawi, [8]University of North Carolina Project–Malawi, Lilongwe, Malawi, [9]Stellenbosch University, Cape Town, South Africa, [10]DLH Corporation, Silver Springs, MD, USA, [11]Northwestern University, Chicago, IL, USA, [12]Office of the Global AIDS Coordinator, Washington, DC, USA, [13]University of Nebraska Medical Center, Omaha, NE, USA*

**Background:** Expanding access to contraception is essential to prevent pregnancy-related health risks for women with TB. Levonorgestrel (LNG) for emergency contraception (EC) is metabolized via cytochrome P450 (CYP) 3A4 and rifampicin (RIF), a potent CYP3A4 inducer, reduces LNG exposure by 57%. Obesity also decreases LNG exposure by 50%. Some guidelines recommend doubling the LNG EC dose when taken with CYP3A4 inducers, but this has not been evaluated in clinical studies with RIF. We hypothesized that doubling the LNG EC dose during RIF therapy would result in similar PK exposure compared to standard dose LNG in the absence of a drug-drug interaction (DDI).

**Methods:** ACTG A5375 was a multicenter, parallel group, PK trial of pre-menopausal females, ≥16 years old, without an indication for EC at entry. Participants without HIV taking RIF on continuation phase of TB therapy received LNG 3mg (n=34) and were compared to participants with HIV on DTG-based ART who received LNG 1.5mg (n=32; control group). Plasma was collected prior to a single dose of LNG, then 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48h post-dose. LNG concentrations were measured by LC-MS/MS and PK parameters calculated by non-compartmental methods. Appropriateness of the DTG as the control group was confirmed by comparison to historical LNG PK data. PK parameters were compared between groups by geometric mean ratio (GMR; 90% CI) adjusted for baseline BMI. Participants were followed for 4 weeks to assess adverse events (AE).

**Results:** All participants (n=66) self-identified as cis-women, 54 (82%) Black, 6 (9%) Latina, and 4 (6%) Asian and enrolled between May 2019 and Nov 2020. BMI was lower in the RIF group compared to the control group, [mean (SD): 22.4 (4.9) vs 26.1 (7.1) kg/$m_2$, p=0.01]. Table 1 summarizes LNG PK parameters. LNG AUCs over 8 and 24 hours were similar between groups. The $C_{max}$ was 27% higher while the $T_{1/2}$ was 57% shorter in the RIF group, resulting in 82% lower Clast and 21% lower AUC48h compared to the control group. Three participants (2 RIF group; 1 DTG group) reported Grade 2/3 LNG-related AEs (nausea and menstrual symptoms)

**Conclusion:** Dose adjustment of LNG EC from 1.5mg to 3mg in those on RIF-based TB therapy resulted in similar or higher LNG exposure over the first 24 hours compared to the control group. RIF therapy shortened the LNG half-life, resulting in lower exposure after 48 hours. Since $C_{max}$ is associated with EC effectiveness, these data support dose-adjustment of LNG EC to 3mg in those taking RIF.

Table 1: LNG pharmacokinetic parameters measured over 48 hours in combination rifampicin-containing TB therapy (RIF group) or with DTG-based ART (Control Group).

| | Median (Q1, Q3) | | Adjusted[2] Geometric Mean Ratio (90% CI) |
|---|---|---|---|
| | LNG 3.0mg + RIF-containing TB therapy[1] (RIF group); (n=34) | LNG 1.5mg + DTG-based ART (Control group) (n=32) | RIF: Control |
| $C_{max}$ (ng/mL) | 28.0 (23.0, 39.6) | 18.7 (14.1, 26.2) | 1.27 (1.09, 1.49) |
| $C_{last}$ (ng/mL)[3] | 0.5 (0.2, 1.0) | 2.8 (1.5, 3.7) | 0.18 (0.11, 0.27) |
| $T_{1/2}$ (h) | 9.0 (6.7, 11.9) | 24.0 (20.0, 28.0) | 0.43 (0.39, 0.48) |
| $AUC_{0\text{-}8h}$ (h*ng/mL) | 124.4 (87.1, 168.8) | 80.5 (66.6, 125.0) | 1.16 (0.99, 1.36) |
| $AUC_{0\text{-}24h}$ (h*ng/mL) | 213.7 (148.6, 283.2) | 157.6 (132.3, 282.3) | 0.96 (0.79, 1.17) |
| $AUC_{0\text{-}48h}$ (h*ng/mL) | 242.7 (181.6, 322.0) | 224.8 (178.3, 400.9) | 0.79 (0.63, 0.97) |

[1]Continuation phase of TB therapy; weight-based RIF dosing per local standard of care + isoniazid +/- ethambutol.
[2]Adjusted for BMI
[3]Clast = The sample collected 48 hours post dose except for 1 participant in the Control group with the concentration at T=24h.

## 78 DTG PK IN PEOPLE WITH HIV RECEIVING DAILY 1HP FOR LATENT TB TREATMENT (ACTG A5372)

Late Breaking

**Marjorie Z. Imperial**[1], Annie Luetkemeyer[1], Rodney Dawson[2], Yoninah Cramer[3], Sue Rosenkranz[3], Susan Swindells[4], Irina Gelmanova[5], Anchalee Avihingsanon[6], Roberto C. Arduino[7], Wadzanai Samaneka[8], Kelly Dooley[9], Rada Savic[1], Anthony T. Podany[4]

*[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Cape Town, Cape Town, South Africa, [3]Harvard TH Chan School of Public Health, Boston, MA, USA, [4]University of Nebraska Medical Center, Omaha, NE, USA, [5]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [6]Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [7]University of Texas at Houston, Houston, TX, USA, [8]University of Zimbabwe, Harare, Zimbabwe, [9]The Johns Hopkins University, Baltimore, MD, USA*

**Background:** The 28-day regimen of daily rifapentine (RPT) + isoniazid (INH) known as 1HP is an effective, ultrashort option for latent TB treatment in people with HIV (PWH). RPT is a known inducer of drug metabolizing enzymes and may decrease dolutegravir (DTG) concentrations and increase the risk of virologic failure. A5372 evaluates the effect of 1HP on the pharmacokinetics (PK) of DTG.

**Methods:** A5372 is a multicenter, PK study in which adult PWH on DTG-containing ART with HIV viral load <50 copies/mL and an indication for latent TB treatment received daily RPT/INH (600mg/300mg) for 28 days. DTG was increased to 50mg twice daily during 1HP treatment. Intensive PK sampling was performed on day 0 (before RPT/INH) with participants on standard DTG 50mg once daily, and on day 28 with participants taking 1HP and DTG 50mg twice daily. Plasma was collected pre-dose, 1, 2, 4, 8, 12, 13, 14, 23, and 24 hours post-DTG dose. Sparse trough sampling occurred on days 3, 14, and 21. Participants were followed for a total of 42 days. DTG concentrations were analyzed by a validated LC-MS/MS method. PK and demographics were summarized as median (Q1, Q3).

**Results:** Thirty-seven participants enrolled between February and November 2021. At the time of this interim analysis, twenty-five participants (44% cisgender female; 56% Black/African; median age 41 (32, 49) years) had PK concentrations available. The median observed DTG trough concentration was 1745 ng/mL (1099, 2694) on day 0 vs. 2146 (1412, 2484) on day 28. Median DTG trough concentrations at days 3, 14, and 21 were 4454, 2127, and 2593 ng/mL, respectively (Figure). Twenty-four of 25 had HIV RNA levels <50 copies/mL at day 28. One participant had an HIV viral load of 160 copies/mL at day 28 (DTG concentration was 2162 ng/mL), with repeat viral load of <50 copies/mL on day 42. One participant exhibited grade 3 ALT and AST on study treatment. No one experienced hypersensitivity. No serious adverse events were reported.

**Conclusion:** DTG trough concentrations with 50mg twice daily dosing during 28 days of daily RPT/INH were higher, not lower, than those with standard dose DTG once daily alone. A decrease in trough concentrations from day 3 to 28 is suggestive of a time dependent induction of DTG metabolism by RPT/INH. These interim PK, virologic suppression, and safety data provide evidence for twice daily DTG in combination with the 1HP regimen.

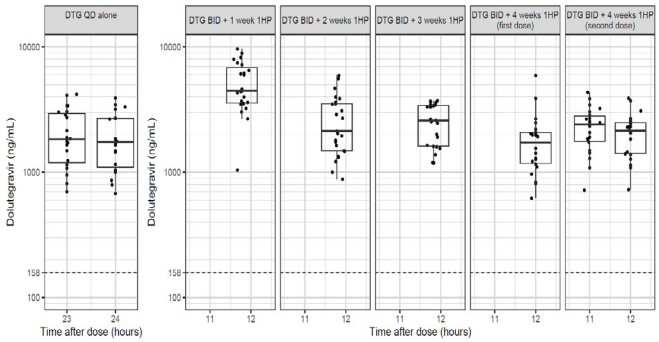



**Figure** – Dolutegravir (DTG) trough concentrations before and during 1HP administration. Day 3 concentrations reported as week 1, day 14 as week 2, day 21 as week 3 and day 28 as week 4.

## 79 TB-PRACTECAL RESULTS: 24 WEEK ALL-ORAL REGIMENS FOR RIFAMPICIN RESISTANT TUBERCULOSIS

Late Breaking

**Bern-Thomas Nyang'wa**[1], Emil Kazounis[2], Ilaria Motta[1], Matthew Dodd[3], Katherine Fielding[3], Catherine Berry[2]

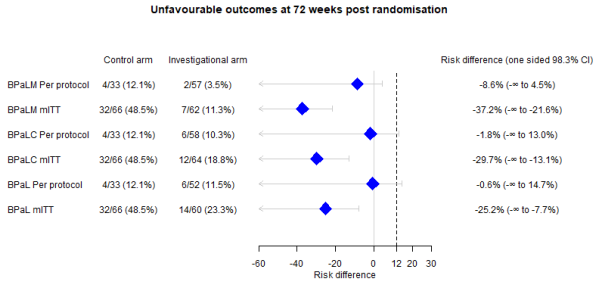
*[1]Médecins Sans Frontières, Amsterdam, Netherlands, [2]Medecins Sans Frontieres, London, UK, [3]London School of Hygiene & Tropical Medicine, London, UK*

**Background:** TB-PRACTECAL (NCT02589782) is a two-stage, multi-arm, randomised, controlled, open label phase II/III clinical trial evaluating the safety and efficacy of three 24-week all-oral regimens for the treatment of rifampicin resistant tuberculosis. We present results comprising all three investigational arms.

**Methods:** Adults and children above 15 years were enrolled into the trial from six sites in Uzbekistan, Belarus and South Africa. Participants were randomised to receive one of three investigational regimens or the control. BPaL arm consisted of bedaquiline 400mg daily for 2 weeks then 200mg three times a week for 22 weeks, pretomanid 200mg daily for 24 weeks and tapered dose linezolid 600mg daily for 16 weeks then 300mg for 8 weeks. Clofazimine 100mg daily for 24 weeks was added in BPaLC arm or Moxifloxacin 400mg daily for 24 weeks in BPaLM arm. All participants were planned for follow up to 108 weeks post randomisation. The primary outcome was the percentage of patients with a composite unfavourable outcome (treatment failure, death, treatment discontinuation, recurrence, loss to follow-up) at 72 weeks post-randomisation. The non-inferiority margin was 12%.

**Results:** Enrolment started in January 2017 and was terminated early for benefit in March 2021. 152 (37%, 27%), 123 (47%, 33%), 126 (33%, 26%) and 151 (44%, 25%) participants (% female, % HIV) were randomised to the Control, BPaL, BPaLC and BPaLM arms respectively. In the modified intention to treat population, the percentage of unfavourable outcomes were 48.5% for the Control, 23.3% for BPaL, 18.8% for BPaLC and 11.3% for BPaLM (see figure 1 for details). There were three recurrencies in BPaL, one in BPaLC and none in BPaLM. Secondary analyses at 24, 48 and 108 weeks post-randomisation were consistent with the primary outcomes. One participant died in BPaLC arm, two in the Control and none in BPaLM and BPaL arms. Participants experiencing at least one grade ≥3 and/or serious adverse event were 58.9%, 21.7%, 31.9%,19.4% in the Control, BPaL, BPaLC and BPaLM respectively. The mean QTcF prolongation from baseline at 24 weeks was 44.9ms, 23.3ms, 40.2ms and 27.0ms for the Control, BPaL, BPaLC and BPaLM arms respectively.

**Conclusion:** 24 week all oral regimens containing a backbone of bedaquiline, pretomanid and tapered dose linezolid are both safe and efficacious in the treatment of rifampicin resistant tuberculosis.




## 80 LONG-ACTING INJECTABLE FOR PREVENTION OF HIV AND UNPLANNED PREGNANCY

New Investigator Scholar

**Isabella Young**[1], Aryani Pallerla[1], Panita Maturavongsadit[1], Alka Prasher[1], Roopali Shrivastava[1], Stephanie Montgomery[1], Amanda Schauer[1], Mackenzie L. Cottrell[1], Angela Kashuba[1], Soumya R. Benhabbour[1]

*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

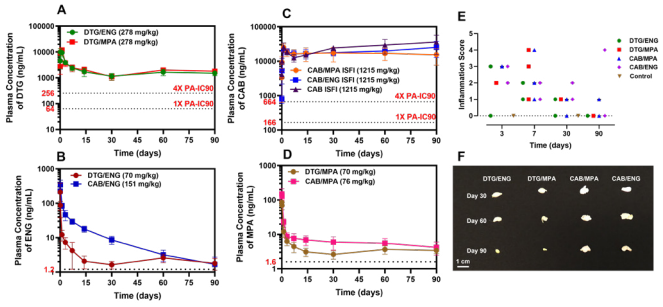
**Background:** Globally 38 million people are living with HIV and half of all pregnancies are unplanned. There is an urgent need to control and prevent these global health crises as current preventative daily oral dosing regimens elicit low patient adherence. Thus, we propose to develop an injectable long-acting, biodegradable, and removable in-situ forming implant (ISFI) as a multipurpose prevention technology (MPT) for the prevention of HIV and unplanned pregnancy.

**Methods:** ISFIs were generated by co-formulating PLGA, NMP, or DMSO, and APIs in a stable solution or suspension. ISFIs were loaded with one of two ARVs, dolutegravir (DTG) or cabotegravir (CAB), and one of two contraceptives,

etonogestrel (ENG) or medroxyprogesterone acetate (MPA). A 90-day pharmacokinetic (PK) and safety study was conducted in female BALB/c mice with optimized MPT ISFI formulations. Mice (n=12/group) were injected subcutaneously with 50 µL of MPT ISFI formulations. Plasma samples were collected longitudinally to quantify drug concentration and TNF-α and IL-6 levels. At day 3, 7, 30, and 90, the depot and surrounding tissue were removed for H&E staining to assess local inflammation. At day 90, depots were removed to quantify residual drug, evaluate polymer degradation with gel permeation chromatography (GPC), and depot microstructure with SEM.

**Results:** In vivo plasma concentrations of CAB and DTG were well above their 4× PA-$IC_{90}$ for 90 days, demonstrated zero-order release kinetics, and showed no differences in drug release when formulated with either hormone. Furthermore, plasma concentrations of ENG and MPA were at, or above target levels based on their marketed products (Nexplanon® and Depo-Provera®) for 90 days and MPA demonstrated zero-order release kinetics. All formulations had mild to moderate inflammation scores with low concentrations of TNF-α (0-3 pg/mL) and IL-6 in plasma (0-20 pg/mL). Depots retrieved 90 days post euthanasia reached ~47% degradation based on GPC analysis and contained ~5% ENG, ~20% DTG, 14-70% MPA and ~85% CAB remaining.

**Conclusion:** Here we report a first-in-line biodegradable, removable, and injectable MPT that elicits a clinically translational drug regimen. Our results demonstrated (1) the ability to co-formulate an ARV (DTG or CAB) and contraceptive (ENG or MPA) in a single ISFI, (2) sustained and target drug release kinetics in vivo for 90 days and (3) all formulations were safe and well-tolerated. Future studies include assessing PK and efficacy in non-human primates.




(A)-(D) In vivo drug concentrations (mean ± standard deviation). PK parameters obtained through non-compartmental analysis. Dotted lines demonstrate target in vivo plasma levels. (E) Skin microscopic inflammation scores of depot and surrounding subcutaneous tissue. (F) Visual representation of retrieved depots and degradation 90 days post-injection.

## 81 PHASE I STUDY OF COMBINATION ANTI-HIV NEUTRALIZING ANTIBODIES IN HIV-NEGATIVE ADULTS

**Magdalena E. Sobieszczyk**[1], Sharon Mannheimer[2], Yunda Huang[3], Carmen Paez[3], Theresa Gamble[4], Deborah A. Theodore[5], Wairimu Chege[6], Margaret Yacovone[6], Chenchen Yu[7], Lily Zhang[7], Jack Heptinstall[8], Kelly E. Seaton[9], Georgia Tomaras[9], David Montefiori[8]

*[1]Columbia University, New York, NY, USA, [2]Mailman School of Public Health, Columbia University, New York, NY, USA, [3]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [4]FHI 360, Durham, NC, USA, [5]Columbia University Medical Center, New York, NY, USA, [6]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [8]Duke University Medical Center, Durham, NC, USA, [9]Duke University School of Medicine, Durham, NC, USA*

**Background:** Multiple broadly neutralizing antibodies (bNAbs) that target different HIV envelope (Env) epitopes are being evaluated for HIV prevention. Combinations of complementary or multi-specific bNAbs are likely needed to effectively prevent HIV acquisition. We present the results of a Phase I clinical trial of dual or triple combinations of four bNAbs (VRC07-523LS, targeting Env CD4 binding site; PGDM1400, V2 glycan; PGT121 and 10-1074, V3 glycan) administered intravenously (IV) to healthy HIV-negative adults.

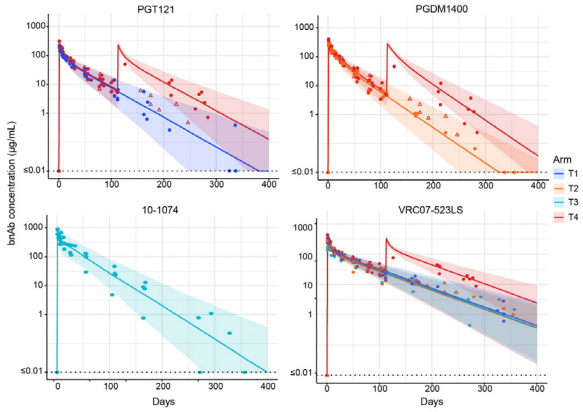
**Methods:** HIV Vaccine Trials Network (HVTN) 130/HIV Prevention Trials Network (HPTN) 089 evaluated the safety, pharmacokinetics (PK) and functional activities of bNAbs administered sequentially at 20 mg/kg per product in dual: PGT121 and VRC07-523LS (Treatment 1 [T1]), PGDM1400 and VRC07-523LS (T2), or 10-1074 and VRC07-523LS (T3); or triple combination: PGDM1400, PGT121 and VRC07-523LS (T4). Serum bNAb levels prior to and following administration of each combination were quantified by validated Binding Antibody Multiplex or ELISA assays. In vivo serum neutralization was assessed as the 50% or 80% inhibitory dilution (ID50, ID80) titer with Env-pseudotyped viruses in the TZM-bl assay. Combination bNAb neutralization interactions were assessed using the Maximum, Additive and Bliss-Hill models.

**Results:** Twenty-seven participants enrolled (median age 26 [range 19-50]; 59.3% female; 70.4% non-Hispanic white, 11.1% Hispanic, 7.4% non-Hispanic Black). Infusions were generally well tolerated. PGT121, PGDM1400, 10-1074, and VRC07-523LS had median elimination half-lives of 30.5, 24.5, 25.8, and 47.9 days, respectively; there were no differences in PK patterns for PGT121, PGDM1400 and VRC07-523LS between the dual or triple combinations. Population PK models fit the concentration profiles well for all bNAbs, with most observed concentrations in the 90% prediction intervals (Figure). The TZM-bl assay revealed greater neutralization magnitude and breadth of the triple versus dual bNAb combinations. Combination bNAb titers were best predicted by the Bliss-Hill model based on individual bNAb neutralization titers.

**Conclusion:** Sequential administration of dual and triple bnAb combinations was safe and well tolerated. PK profiles of each bNAb in combination were consistent with prior data for each bNAb and across treatment arms, and there was no loss of complementary neutralization magnitude or breadth in vivo. These data will inform the design of future combination bNAb HIV prevention efficacy trials.

**Figure. Observed (symbols) and predicted (curves) PGT121, PGDM1400, 10-1074 and VRC07-523LS serum concentrations with 90% prediction interval from the population PK model (shaded areas).**

*Non-linear mixed effects two-compartmental PK modeling was used to fit the observed serum concentrations of each bnAb. For a given bnAb, PK data collected from both the dual and triple combinations, if applicable, were pooled for the PK modeling. Treatment arms: single dose of PGT121T1 and VRC07-523LS (T1); single dose of PGDM1400 and VRC07-523LS (T2); single dose of 10-10-74 and VRC07-523LS (T3); and two doses (at baseline and 4 months) of PGT121, PGDM1400, and VRC07-523LS (T4). Serum bnAb levels prior to and following administration of each combination were simultaneously quantified by a validated Binding Antibody Multiplex Assay (VRC07-523-LS, PGDM1400, PGT121) or by validated ELISA (10-1074).*




## 82 PHASE I PK, SAFETY, AND ACCEPTABILITY STUDY OF A 90-DAY TENOFOVIR VAGINAL RING

**Albert Liu**[1], Holly Gundacker[2], Barbra A. Richardson[2], Beatrice Chen[3], Craig Hoesley[4], Ariane Van der Straten[5], May Beamer[3], Jennifer Robinson[6], Cindy Jacobson[3], Rachel Scheckter[7], Katherine Bunge[3], Andrea Thurman[8], Gustavo Doncel[8], Jeanna Piper[9], Mark Marzinke[6]

*[1]San Francisco Department of Public Health, San Francisco, CA, USA, [2]Statistical Center for HIV/AIDS Research and Prevention, Seattle, WA, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]University of Alabama at Birmingham, Birmingham, AL, USA, [5]Astra Consulting, Kensington, CA, USA, [6]The Johns Hopkins University, Baltimore, MD, USA, [7]FHI 360, Durham, NC, USA, [8]Contraception Research and Development, Arlington, VA, USA, [9]National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA*

**Background:** Vaginal rings are promising for long-acting HIV prevention. Extended duration rings may reduce user burden, cost, and encourage adherence. We evaluated the safety, pharmacokinetics (PK), adherence, and acceptability of a 90-day tenofovir (TFV) vaginal ring.

**Methods:** MTN-038 enrolled 49 HIV-negative participants into a Phase I, multi-site, randomized (2:1) trial comparing a 90-day ring containing 1.4 grams (g) TFV used continuously to a placebo ring. TFV concentrations were quantified in plasma, cervicovaginal fluid (CVF), rectal fluid, and cervical tissue, and TFV-diphosphate (TFV-DP) in cervical tissue. Used rings were analyzed for residual TFV levels. Safety was assessed by adverse events (AEs); acceptability and adherence by self-report.

**Results:** Mean age was 29.4 (range 18-43) years; 22% were Black, 53% white, 10% Asian, and 14% mixed/other race. Retention was 98% through day 91, and 84% reported being fully adherent. There were no differences in the proportion of participants with grade ≥2 genitourinary AEs in the TFV vs. placebo arms (p=0.41); no grade ≥3 AEs were reported. Geometric mean TFV concentrations and PK parameters are shown in the Table. $T_{max}$ was 34 days for CVF and rectal fluid, with mean TFV concentrations declining at day 91. Geometric mean TFV-DP tissue concentrations exceeded the 1,000 fmol/mg target through day 56, but fell to 456 fmol/mg by day 91. Mean and median residual TFV concentrations in used rings were 0.29 and 0.15 g respectively (IQR 0.00-0.58 g). Among 32 returned rings, 13 had no or low (<0.1 g) residual TFV. Participants with no/low residual TFV had lower geometric mean TFV concentrations in CVF (11 vs. 2471 ng/mg) and lower cervical tissue concentrations of TFV (0.1 vs. 72 ng/mg) and TFV-DP (12 vs. 3296 fmol/mg) at day 91 vs. those with higher residual TFV (all p<0.001), however concentrations at earlier time points were not significantly different between groups. Residual TFV in returned rings did not differ by sociodemographics, sexual activity, or baseline Nugent Score. A majority of participants reported liking the ring (median (IQR): 8 (7-9) on 10-point Likert scale) and reported high likelihood of using the ring in the future, if effective (median (IQR): 9 (7-10)).

**Conclusion:** The 90-day TFV ring was well-tolerated, acceptable, and exceeded target cervical tissue concentrations through day 56, but declined thereafter. Additional studies should characterize the higher release from TFV rings in some participants and the optimal duration of use.

**Table: Geometric Mean Tenofovir Concentrations and PK parameters in Plasma, Cervicovaginal Fluid, Rectal Fluid and Cervical Tissue.**

| | TFV in Plasma (CV%) (ng/mL) | TFV in CVF (CV%) (ng/mg) | TFV in Rectal Fluid (CV%) (ng/mg) | TFV in Cervical Tissue (CV%) (ng/mg)[1] | TFV-DP in Cervical Tissue (CV%) (fmol/mg)[1] |
|---|---|---|---|---|---|
| Day 1 | 0.64 (131%) | 438 (75%) | 0.29 (1111%) | -- | -- |
| Day 7 | 1.92 (102%) | 1468 (130%) | -- | -- | -- |
| Day 14 | 3.58 (115%) | 2006 (57%) | 0.70 (583%) | 45.9 (11800%) | 2680 (83%) |
| Day 28 | 5.04 (235%) | 2012 (289%) | 0.90 (1356%) | 39.1 (323%) | 3218 (86%) |
| Day 56 | 7.86 (140%) | 2817 (71%) | 1.38 (476%) | 37.1 (177%) | 1893 (178%) |
| Day 91, prior to removal | 1.81 (612%) | 271 (24859%) | 0.46 (1093%) | 6.5 (254896%) | 456 (16736%) |
| Day 91, 4 h post removal | 1.08 (427%) | 41.3 (4067844%) | 0.42 (4316%) | -- | -- |
| Day 92, 24 h post removal | 0.24 (127%) | 7.2 (85,571%) | -- | -- | -- |
| $C_{max}$ | 11.98 (121%) | 3853 (59%) | 5.88 (1064%) | -- | -- |
| $T_{max}$ (days) | 59 (54%) | 33.5 (106%) | 33.6 (157%) | -- | -- |
| AUC (0-92) | 599.08 (99.9%) | 216,079 (49%) | 167.27 (404%) | -- | -- |

CV=coefficient of variation; $C_{max}$, peak concentration; $T_{max}$, time to peak concentration; AUC, area under the concentration time curve from 0-92 days
[1]n=15 for day 14 and day 56 biopsies; n=17 for day 28 and day 91 biopsies

## 83 ISLATRAVIR DISTRIBUTION IN MUCOSAL TISSUES, PBMC, & PLASMA AFTER MONTHLY ORAL DOSING

**Craig W. Hendrix**[1], Sharon L. Hillier[2], Linda-Gail Bekker[3], Sharlaa Badal-Faesen[4], Sharon A. Riddler[5], Edward J. Fuchs[1], Pippa J. Macdonald[3], Stacey Edick[6], Rebeca M. Plank[7], Cynthia M. Chavez-Eng[7], Barbara Evans[7], Xiaowei Zang[7], Ryan Vargo[7], Michael N. Robertson[7], Munjal Patel[7]

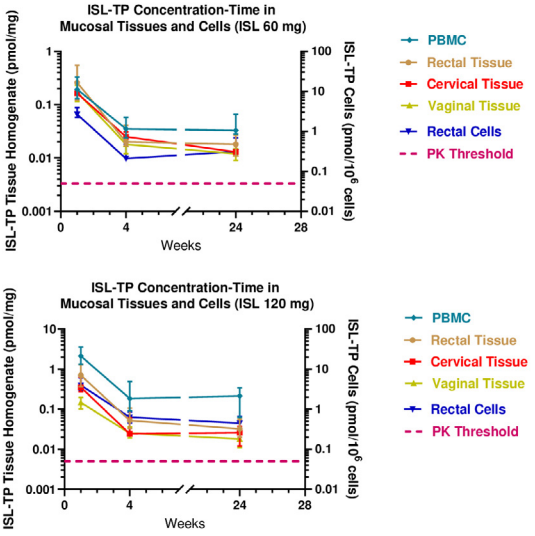
*[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]Magee–Womens Research Institute, Pittsburgh, PA, USA, [3]Desmond Tutu HIV Foundation, Cape Town, South Africa, [4]University of Witwatersrand, Johannesburg, South Africa, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]University of Pittsburgh Medical Center, Pittsburgh, PA, USA, [7]Merck & Co, Inc, Kenilworth, NJ, USA*

**Background:** Islatravir (ISL), a novel nucleoside analogue with multiple mechanisms of action, has the potential to be an important new agent for HIV-1 pre-exposure prophylaxis (PrEP) due to its potent HIV-1 antiviral activity and long intracellular half-life. We evaluated ISL PK in blood and mucosal tissues (rectal, vaginal, and cervical) after monthly (QM) oral dosing; evaluation of terminal phase PK is ongoing.

**Methods:** This exploratory tissue PK sub-study is part of a Phase IIa, randomized, double-blind, placebo-controlled, multicenter trial of QM ISL (60 mg, 120 mg, or matching placebo) in adults at low-risk for HIV-1 acquisition (NCT04003103). We collected plasma, peripheral blood mononuclear cells (PBMC), and cervical, vaginal, and rectal tissue samples at study Weeks 1 and 4 (1 and 4 weeks, respectively, after the first dose) and at study Week 24 (4 weeks after the last [6th] dose of study intervention). Tissue samples were processed to homogenates (and also to cell lysates for rectal samples). All samples were assayed by liquid chromatography with tandem mass spectrometry. Intercompartmental ratios and paired samples correlations were assessed.

**Results:** We enrolled 54 participants (21 in US, 33 in South Africa; 41 females). Mean age was 32 years and mean baseline weight was 81 kg. Following ISL administration, ≥95% of samples had quantifiable parent ISL and ≥88% had ISL-triphosphate (ISL-TP) across all tissues and time points. ISL-TP trough concentrations were comparable across cervical, vaginal, and rectal tissues (Figure). Plasma ISL and ISL-TP in cervical, vaginal, and rectal tissues were highly correlated (adjusted R2 ≥0.7, p<0.001); ISL-TP across tissue types and across rectal matrices were also strongly correlated (adjusted R2 ≥0.6, p<0.001). The average ratio of ISL-TP between PBMCs and rectal cells at Week 4 was ~5-8. Week 4 ISL-TP in PBMC and in rectal cells exceeded the PK threshold for prophylaxis (0.05 pmol/$10_6$ PBMC) by >20 and >4 fold, respectively. Our findings suggest the PBMC-based PK threshold was achieved in all target tissues, given correlations within rectal matrices and similarities among all tissue homogenates.

**Conclusion:** ISL and ISL-TP were measurable and comparable in cervicovaginal and rectal tissues suggesting that ISL distributes similarly to these tissues and is present in its active, phosphorylated form (ISL-TP). Systemic ISL PK can be used as a surrogate for tissue exposures.




**Notes: Tissue samples were collected at study Weeks 1 and 4 (1 and 4 weeks, respectively, after the first monthly oral [QM] dose) and study Week 24 (4 weeks after the last [6th] QM dose).Tissues (rectal,cervical and vaginal) and rectal cells represent median (inter quartile range);PBMC represents median ($5^{th}$-$95^{th}$ percentile); PK threshold represents 0.05 pmol/$10^6$ PBMC.**

## 84 THE BIDIRECTIONAL EFFECTS OF HORMONE THERAPY AND PrEP IN TRANSGENDER INDIVIDUALS

**Jill Blumenthal**[1], Ravi Goyal[2], Leah Burke[1], Michael Dubé[3], Martin Hoenigl[1], David J. Moore[1], Karen Chow[1], Jordan Silva[1], Katya Corado[4], Richard H. Haubrich[5], Peter Anderson[6], Robert Bolan[7], Sheldon Morris[2]

*[1]University of California San Diego, San Diego, CA, USA, [2]University of California San Diego, La Jolla, CA, USA, [3]University of Southern California, Los Angeles, CA, USA, [4]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA, [5]Gilead Sciences, Inc, Foster City, CA, USA, [6]University of Colorado, Aurora, CO, USA, [7]Los Angeles LGBT Center, Los Angeles, CA, USA*

Background: The bi-directional effects of hormone therapy (HT) and preexposure prophylaxis (PrEP) among transgender (TG) individuals have been examined but the evaluation periods have been short with small cohorts and mixed results.

**Methods:** The iTAB plus Motivational Interviewing for PrEP Adherence in Transgender Individuals (ImPrEPT) study was a parallel two arm RCT of adherence in TG individuals, using individualized Texting for Adherence Building (iTAB) with and without brief motivational interviewing over 48 weeks for PrEP adherence. Individuals agreeing to participate in the hormone sub-study had tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) and sex hormones in serum measured at weeks 0 and 12 and surveys about desired hormone effects and satisfaction with HT at weeks 0 and 24. For this analysis, TG women and non-binary individuals assigned male at birth were grouped as transgender women (TGW) and TG men and non-binary individuals assigned female at birth were grouped as transgender men (TGM). Wilcoxon statistical tests and linear regression adjusting for confounding factors were used to determine differences in TFV-DP in TG on and off HT as well as hormone concentrations and changes in satisfaction with HT gender-affirming traits over time.

**Results:** Between 6/2017 and 9/2020, 255 TG individuals were randomized in the main study with n=172 individuals enrolling in the hormone sub-study. Mean age was 38 (range 18-58) with 15% Black, 44% White and 34% Latinx. Among 91 TGW on stable estrogen, estradiol concentrations did not change significantly between Week 0 and 12 in individuals taking PrEP (252.4 vs 222.3 pg/mL, p=0.81). Among 60 TGM on stable testosterone, total testosterone concentrations did not change significantly between Week 0 and 12 in individuals taking PrEP (352.7 vs 266.2 ng/dL, p=0.84). At week 12, there

was no difference in TFV-DP in TGW not taking HT (n=28) compared to taking HT (n=75) (est. difference of -27.3 fmol/p, p=0.89), and TGM not taking HT (n=11) compared to taking HT (n=43) (est. difference of 505.3 fmol/p, p=0.17), adjusting for confounding factors. There were no changes in satisfaction with or desired physical effects from HT on gender transition (Table 1).

**Conclusion:** Transgender individuals both on and off HT had similar TFV-DP concentrations in DBS after 12 weeks of daily reported FTC/TDF PrEP use. Serum hormone concentrations were not affected by FTC/TDF PrEP use, and there were no changes in the perceived effect on HT in those taking PrEP.

Table 1. PrEP Drug Concentrations and Body Satisfaction Scores by Gender Identity

| | Transgender Women (n=112) | p-value | Transgender Men (n=60) | p-value |
|---|---|---|---|---|
| Week 12 TFV-DP Concentration, fmol/punch (SD)* | | 0.45 | | 0.20 |
| No hormone therapy | 1885.8 (1058.7) (n=28) | | 1631.6 (769.4) (n=11) | |
| Yes hormone therapy | 1641.2 (797.4) (n=75) | | 2029.3 (943.9) (n-43) | |
| Body Image Satisfaction (SD)** | | 0.83 | | 0.11 |
| Week 0 | 2.7 (0.80) (n=23) | | 2.2 (0.60) (n=11) | |
| Week 24 | 2.6 (0.91) (n=19) | | 1.84 (0.62) (n=10) | |
| Satisfaction with HT on gender transition (SD)*** | | 0.35 | | 1.0 |
| Week 0 | 1.9 (1.04) (n=23) | | 1.5 (0.69) (n=11) | |
| Week 24 | 1.9 (0.89) (n=19) | | 1.6 (0.84) (n=10) | |

TFV-DP= tenofovir-diphosphate; SD= standard deviation; HT= hormone therapy
*Adjusting for confounding factors age, creatinine clearance and weight.
**Body Image Satisfaction summed 5 questions about desired physical effects from HT (low score is 1, high score is 5)
***Satisfaction with HT on gender transition is based on question "how satisfied are you with your HT on your gender transition?" (low score is 1, high score is 5)

## 85 PHASE IIA TRIAL OF ISLATRAVIR QM FOR HIV PrEP: WEEK 24 METABOLIC AND RENAL OUTCOMES

**Pippa J. Macdonald**[1], Sharon A. Riddler[2], Sharlaa Badal-Faesen[3], Howard Schwartz[4], Johannes Lombaard[5], Yoseph Caraco[6], Avivit Peer[7], Ciaran McMullan[8], Keith D. Kaufman[8], Brenda Homony[8], Katherine Nedrow[8], Valerie Teal[8], Michael N. Robertson[8], Rebeca M. Plank[8]

*[1]Desmond Tutu HIV Centre, Cape Town, South Africa, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa, [4]Research Centers of America, Hollywood, FL, USA, [5]Josha Research, Bloemfontein, South Africa, [6]Hadassah Medical Center, Jerusalem, Israel, [7]Rambam Health Care Campus, Hafia, Israel, [8]Merck & Co, Inc, Kenilworth, NJ, USA*

**Background:** Adverse events (AEs) and long-term toxicities, including weight gain, loss of bone mineral density (BMD), and changes in renal function, have been reported among persons taking approved HIV-1 pre-exposure prophylaxis (PrEP) regimens. Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor under clinical investigation for the treatment and prevention of HIV-1. ISL has a long half-life and a pharmacokinetic profile compatible with extended-duration dosing regimens. Here we present metabolic and renal outcomes through Week 24 of a Phase IIa trial of ISL 60 mg, ISL 120 mg, or matching placebo, all dosed once monthly (QM).

**Methods:** This randomized, double-blind, placebo-controlled, parallel-group, multi-center trial (Israel, South Africa, and USA) assessed the safety, tolerability, and pharmacokinetics of monthly oral ISL in adults (age 18-65 years) at low-risk for HIV-1 acquisition (NCT04003103). Participants were randomly assigned (2:2:1) to receive a total of 6 QM doses of ISL 60 mg, ISL 120 mg, or matching placebo. Metabolic outcomes (weight, total hip BMD, lumbar spine BMD, peripheral fat, trunk fat) and renal outcomes (serum creatinine, estimated glomerular filtration rate [eGFR], retinol-binding protein/creatinine ratio) were assessed through Week 24. Median percent change from baseline and interquartile range (IQR) were determined.

**Results:** Of 242 randomized participants (median age, 31 years; male, 33%; White, 53%; Black or African American, 42%), 222 completed dosing and 20 discontinued study intervention prior to Week 24; none discontinued due to metabolic or renal AEs. Median body mass index at baseline for ISL 60 mg, ISL 120 mg, and placebo was 26.8 kg/m$^2$, 25.8 kg/m$^2$, and 26.6 kg/m$^2$, respectively. Median percent changes from baseline in weight, total hip BMD, lumbar spine BMD, peripheral fat, and trunk fat were small and comparable for ISL 60 mg QM and placebo groups, with slight increases in weight, peripheral fat, and trunk fat in the ISL 120 mg QM group (Table). No change in eGFR was observed across treatment groups; small and similar decreases in urinary retinol-binding protein to creatinine ratios were seen across all treatment groups (Table).

**Conclusion:** No clinically meaningful differences from placebo in metabolic and renal parameters were observed with ISL 60 mg or ISL 120 mg after 6 QM doses. Ongoing Phase III clinical trials of ISL 60 mg QM for PrEP will provide additional insights into renal and metabolic outcomes with longer ISL exposures.

**Table. Median Percent Change in Metabolic and Renal Outcomes From Baseline at Week 24.**

| | ISL 60 mg QM (n = 97) % Change (IQR) | n | ISL 120 mg QM (n = 97) % Change (IQR) | n | Placebo QM (n = 48) % Change (IQR) | n |
|---|---|---|---|---|---|---|
| **Metabolic outcomes** | | | | | | |
| Weight | 0.39 (-2.13, 3.55) | 83 | 1.82 (-0.93, 4.40) | 92 | 0.24 (-1.47, 2.84) | 44 |
| Total hip BMD[a] | 0.22 (-0.90, 1.32) | 83 | -0.09 (-1.19, 1.30) | 87 | 0.10 (-1.64, 1.88) | 42 |
| Lumbar spine BMD[a] | 0.53 (-1.37, 1.55) | 82 | 0.00 (-1.38, 1.26) | 89 | 0.63 (-1.39, 1.31) | 42 |
| Peripheral fat[a] | -0.35 (-5.68, 6.07) | 83 | 2.50 (-2.80, 8.10) | 89 | 0.77 (-2.35, 5.15) | 41 |
| Trunk fat[a] | 0.95 (-7.74, 9.17) | 83 | 3.42 (-1.40, 10.47) | 89 | 0.25 (-7.21, 4.78) | 41 |
| **Renal outcomes** | | | | | | |
| Serum creatinine | 0.0 (-11.8, 12.8) | 84 | 0.0 (-5.8, 11.1) | 92 | 0.0 (0.0, 14.3) | 44 |
| eGFR[b] | 0.0 (-12.9, 15.6) | 84 | 0.0 (-11.5, 7.2) | 92 | 0.0 (-14.3, 0.0) | 44 |
| RBP/creatinine | -10.7 (-33.9, 15.2) | 80 | -12.9 (-34.1, 21.9) | 84 | -7.8 (-29.8, 35.0) | 41 |

[a]Measured using dual-energy X-ray absorptiometry.
[b]Calculated by the modification of diet in renal disease equation.
BMD, bone mineral density; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ISL, islatravir; QM, once monthly; RBP, retinol-binding protein.

## 86 COUNTERFACTUAL ESTIMATION OF CAB-LA EFFICACY AGAINST PLACEBO USING EXTERNAL TRIALS

**Deborah Donnell**[1], Fei Gao[1], James Hughes[2], Brett Hanscom[1], Lawrence Corey[1], Myron S. Cohen[3], Srilatha Edupuganti[4], Nyaradzo M. Mgodi[5], Helen V. Rees[6], Jared Baeten[2], Glenda E. Gray[7], Linda-Gail Bekker[8], Mina C. Hosseinipour[3], Sinead Delany-Moretlwe[6]

*[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]University of Washington, Seattle, WA, USA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Emory University, Atlanta, GA, USA, [5]University of Zimbabwe-University of California San Francisco Collaborative Research Program, Chitungwiza, Zimbabwe, [6]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [7]South Africa Medical Research Council, Cape Town, South Africa, [8]Desmond Tutu TB Centre, Western Cape, South Africa*

**Background:** Oral PrEP is effective for HIV prevention in women, but daily adherence has proven challenging. HPTN 084 was an active-control randomized trial comparing oral PrEP (TDF/FTC) to the long-acting antiretroviral cabotegravir (CAB-LA) in women in sub-Saharan Africa. CAB-LA reduced HIV infection rates to very low levels, showing an 89% reduction relative to TDF/FTC, in follow-up between Nov2017-Nov2020. However, efficacy compared to no use of PrEP is unknown. The use of counterfactual placebo measures of incidence has been proposed to assess clinically useful estimates of PrEP efficacy.

**Methods:** We used placebo arm data from women enrolled in three contemporaneous randomized HIV prevention trials to construct estimates of counterfactual (CF) placebo rates of HIV infection and efficacy for CAB-LA against a CF placebo. We construct estimates for each external trial, restricted to countries participating in both trials. Analysis weights were used to match relative person-years by country to HPTN 084 follow-up. The efficacy estimate compares incidence in the CAB-LA arm in HPTN084 to estimated counterfactual incidence, with confidence limits constructed assuming study independence and appropriately incorporating the use of weights. Data for women come from three trials conducted in southern Africa: the ECHO trial, the placebo arms of the AMP trial (HVTN 703/HPTN 081) and an HIV vaccine trial in South Africa (HVTN 702). Three counterfactual estimates were constructed, two in multi-country settings (AMP and ECHO) and one in South Africa (HTVN702). Oral PrEP was part of the standard of prevention in all three studies, but person-time with use of oral PrEP was less than 5%.

**Results:** The placebo counterfactual studies included 637 women from AMP, 7829 from ECHO and 1884 from HVTN702; HPTN 084 had 1614 women in the CAB-LA arm. After analytic weighting, age, marital status and baseline rates of gonorrhea and chlamydia infection were similar between CAB-LA and placebo. Counterfactual placebo HIV incidence rates in women in the multi-country settings were 2.6/100PY (AMP), 4.5/100PY (ECHO) and 4.2/100PY (HVTN702); compared to 0.19/100PY, 0.23/100PY, and 0.28/100PY in the CAB-LA arm, respectively. Estimates of CAB-LA versus placebo efficacy consistently showed CF placebo-based efficacy of 93-95% (Table 1).

**Conclusion:** Counterfactual placebo data from external trials across a range of settings provide strong support for high efficacy of CAB-LA for HIV prevention in women.

Table: Counterfactual placebo estimates of HIV incidence and efficacy compared to CAB-LA in Women

| CF placebo study | Country subgroups included | Trial conduct period | HPTN 084 CAB-LA PY included PY/total PY (%) | CAB-LA HIV Incidence/100 PY | CF Placebo PY included/total PY (%) | CF Placebo HIV Incidence/100 PY (weighted) | Efficacy for CAB-LA vs CF Placebo HR (95% CI) |
|---|---|---|---|---|---|---|---|
| **AMP Women (HVTN 703/HPTN 081) Placebo arm (N = 637)** | Botswana, Kenya, Malawi, South Africa, Zimbabwe | May2016-Apr2020 | 1547/1956 (79%) | 0.19 | 1169/1203 (97%) | 2.62 | 93% (76%-98%) |
| **ECHO (N = 7829)** | eSwatini, Kenya, South Africa | Dec2015-Oct2018 | 856/1956 (44%) | 0.23 | 9594/10456 (92%) | 4.47 | 95% (79%-99%) |
| **HVTN 702 Women Placebo arm (N=1884)** | South Africa | Oct2016-Jun2019 | 723/1956 (37%) | 0.28 | 2782/2782 (100%) | 4.21 | 93% (73%-98%) |

## 87 DIFFERENT HIV PROTECTION FOR TRADITIONAL AND MEDICAL CIRCUMCISION IN HPTN 071(PopART)

New Investigator Scholar

**Kidist B. Zewdie**[1], Michael Pickles[2], Sian Floyd[3], Sarah Fidler[2], Helen Ayles[4], Peter Bock[5], Graeme Hoddinot[6], Nomtha Mandla[5], Ephraim Sakala[7], Kwame Shanaube[7], Musonda Simwinga[4], Estelle M. Piwowar-Manning[8], Richard Hayes[3], Deborah Donnell[9]

*[1]University of Washington, Seattle, WA, USA, [2]Imperial College London, London, UK, [3]London School of Hygiene & Tropical Medicine, London, UK, [4]Zambart, Lusaka, Zambia, [5]Desmond Tutu TB Centre, Western Cape, South Africa, [6]Stellenbosch University, Cape Town, South Africa, [7]University of Zambia, Lusaka, Zambia, [8]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [9]Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

**Background:** An important component of combination prevention is voluntary medical male circumcision (VMMC). Inclusion of traditionally circumcised men in VMMC uptake campaigns may be important if traditional male circumcision, widely practiced in sub-Saharan Africa, is less protective than VMMC against HIV acquisition.

**Methods:** We used survey data from the Population Cohort of the HPTN 071 (PopART) study in South Africa and Zambia. This cluster-randomized trial assessed the impact of a combination prevention package, which included referral for medical male circumcision, on population-level HIV incidence in 21 study communities in Zambia and South Africa. We evaluated the effect of the community level PopART intervention on uptake of VMMC, using a two-stage analysis approach. We used discrete-time survival analysis to evaluate the association between male circumcision (classified as uncircumcised, medical (VMMC), or traditional (TMC)) and HIV incidence.

**Results:** 10,803 HIV-negative men with self-reported circumcision status were included in this study. At baseline, 56% were uncircumcised, 26% were traditionally circumcised and 18% were medically circumcised. The prevalence of TMC and VMMC were different between South Africa and Zambia; 83% of men who reported being medically circumcised were from Zambia, 90% of men who reported traditional circumcision resided in South Africa. 11% of uncircumcised men reported uptake of medical male circumcision during PopART intervention and the adjusted rate ratio in PopART communities compared to standard of care was 1.10 (95% CI 0.82, 1.50, P=0.48), indicating a non-significant 10% higher uptake of VMMC in communities randomized to the PopART intervention. HIV incidence among those who were medically circumcised was 0.31 per 100 person-years (PY), among those traditionally circumcised was 0.94/100 PY and among uncircumcised was 0.97/100 PY. The risk of HIV for medically circumcised men was 70% lower than for those who were uncircumcised adjHR=0.30 (95% confidence interval [CI], 0.16 to 0.55; p<0.0001). There was no difference in risk of HIV acquisition for traditionally circumcised men compared to those uncircumcised adjHR= 0.84 (95% CI 0.54, 1.31; P=0.45).

**Conclusion:** Medical male circumcision is likely to offer increased HIV prevention in men who have undergone traditional circumcision. Household-based delivery of HIV testing followed by referral for medical male circumcision did not result in substantial MMC uptake.

## 88 CHOICE AND ADHERENCE TO DAPIVIRINE RING OR ORAL PrEP BY YOUNG AFRICAN WOMEN IN REACH

Late Breaking

**Kenneth Ngure**[1], Gonasagrie Nair[2], Daniel Szydlo[3], Elizabeth R. Brown[3], Carolyne Akello[4], Pippa Macdonald[5], Thesla Palanee-Phillips[6], Bekezela Siziba[7], Sharon L. Hillier[8], Morgan Garcia[9], Sherri Johnson[9], Lisa Levy[9], Tara McClure[9], Lydia Soto-Torres[10], Connie L. Celum[11]

*[1]Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya, [2]Stellenbosch University, Stellenbosch, South Africa, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [4]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [5]Desmond Tutu HIV Foundation, Cape Town, South Africa, [6]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [7]University of Zimbabwe, Harare, Zimbabwe, [8]University of Pittsburgh, Pittsburgh, PA, USA, [9]FHI 360, Durham, NC, USA, [10]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, [11]University of Washington, Seattle, WA, USA*

**Background:** Adolescent girls and young women (AGYW) account for most new HIV acquisitions in Africa. WHO has recommended oral PrEP and the monthly dapivirine vaginal ring (ring) for women at risk of HIV acquisition. Given the need for high adherence for effectiveness and lower adherence among AGYW in efficacy trials, we assessed choice of and adherence to the ring and oral PrEP among African AGYW in the MTN-034/REACH crossover trial.

**Methods:** REACH enrolled 247 HIV-negative, non-pregnant AGYW ages 16-21 from South Africa, Zimbabwe, and Uganda from February 2019 to April 2021. Participants were randomized to the monthly ring or daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for the first 6 month period, then switched to the other product for the second 6 month period. Participants were given a choice of ring, oral PrEP, or neither in the third 6 month period. Adherence was measured by residual drug levels in returned used rings and dried blood spots (DBS) for oral PrEP, and is shown by proportion of visits. Dapivirine (DPV) release of <0.9mg indicate non-use, 0.9 to >4.0mg some use, and ≥4.0mg consistent with 28 days of use. Tenofovir diphosphate (TFV-DP) levels of <16 fmol/DBS punch indicates no use, 16-700 fmol/punch moderate and ≥700 fmol/punch high adherence. The proportion of visits with high adherence was compared between the cross-over and choice periods for each product.

**Results:** Participants' average age was 18 years, and of 227 (92%) who continued in the choice period, 152 (67%) chose the ring, 71 (31%) oral PrEP, and 4 (2%) neither. Randomization sequence in the crossover period did not influence product choice. Residual DPV levels in used rings and TFV-DP levels in DBS showed participants had some to high use of the ring and moderate to high adherence to oral PrEP with <5% of visits with no adherence (Figure 1). High adherence to oral PrEP in the crossover period was strongly associated with choice of oral PrEP (p<0.001); an association was not observed for rings (p=0.85).

**Conclusion:** In the choice period among African AGYW who had 6 months use of both the ring and oral PrEP, 2/3 opted to use the ring; those with high adherence to oral PrEP in the crossover periods were likely to choose oral PrEP. Drug levels indicate partial to high adherence to both the ring and oral PrEP, higher than in prior studies. AGYW can make informed choices about HIV prevention products and are motivated to continue to use a product of their preference after previous oral PrEP or ring use.

Table: Counterfactual placebo estimates of HIV incidence and efficacy compared to CAB-LA in Women

| CF placebo study | Country subgroups included | Trial conduct period | HPTN 084 CAB-LA PY included PY/total PY (%) | CAB-LA HIV Incidence/100 PY | CF Placebo PY included/total PY (%) | CF Placebo HIV Incidence/100 PY (weighted) | Efficacy for CAB-LA vs CF Placebo HR (95% CI) |
|---|---|---|---|---|---|---|---|
| **AMP Women (HVTN 703/HPTN 081) Placebo arm (N = 637)** | Botswana, Kenya, Malawi, South Africa, Zimbabwe | May2016-Apr2020 | 1547/1956 (79%) | 0.19 | 1169/1203 (97%) | 2.62 | 93% (76%-98%) |
| **ECHO (N = 7829)** | eSwatini, Kenya, South Africa | Dec2015-Oct2018 | 856/1956 (44%) | 0.23 | 9594/10456 (92%) | 4.47 | 95% (79%-99%) |
| **HVTN 702 Women Placebo arm (N=1884)** | South Africa | Oct2016-Jun2019 | 723/1956 (37%) | 0.28 | 2782/2782 (100%) | 4.21 | 93% (73%-98%) |

## 89 TRENDS IN HIV TESTING AND LINKAGE TO HIV TREATMENT IN 41 COUNTRIES, 2016–2021

**Bakary Drammeh**[1], Anindya K. De[1], Amy Medley[1], Randy Yee[2], Shazad Ahmed[2], Helen Dale[1], Arielle Lasry[1], Vincent J. Wong[3], Michael Grillo[4], Emanny Sanchez[1], David A. Miller[1], Tiffiany Aholou[1], Shahul Ebrahim[1], Stephanie Behel[1]

*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]Centers for Disease Control and Prevention, Washington, DC, USA, [3]United States Agency for International Development, Washington, DC, USA, [4]Defense Health Agency, San Diego, CA, USA*

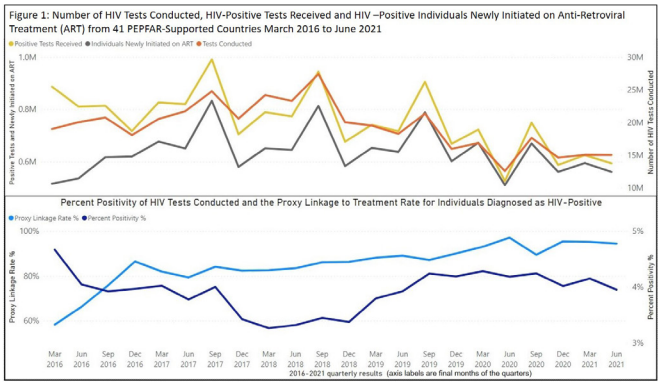
**Background:** Strengthening HIV testing services (HTS) and linkage to antiretroviral therapy (ART) is critical to reaching the UNAIDS 1st 95 and 2nd 95 targets (95% of people living with HIV (PLHIV) know their status, 95% are on ART). In support of these goals, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) updated its technical guidance in 2019 to promote efficient HIV testing strategies to reduce unnecessary tests and improve HIV case finding. Facilitated linkage services and differentiated service delivery were implemented to expand access to and uptake of ART.

**Methods:** We analyzed HIV testing and treatment outcomes reported quarterly to PEPFAR from 41 countries between 2016-2021. A descriptive trend analysis of testing and treatment outcomes from (January–March) 2016 through (April–June) 2021 was conducted for persons aged ≥ 15 years with complete HIV data. Trends analyzed include the number of HIV tests conducted, HIV positive tests, percent positivity (HIV positive tests divided by total tests), number of PLHIV newly initiated on ART, and the proxy patient linkage rate (individuals newly initiated on ART divided by HIV-positive tests).

**Results:** From January 2016 to June 2021, the 41 countries reported conducting 443 million (M) tests, including 17.5M positive tests. The number of tests conducted increased by 42% from 19M in March 2016 to a peak of 27M in

September 2018, before decreasing by 45% to 15M in June 2021 (figure 1). HIV-positive tests increased by 11% from 0.9M in March 2016 to a peak of 1M in September 2017, before decreasing by 40% to 0.6M in June 2021. Percent positivity was stable at approximately 5% from March 2016 to September 2017, decreased to 3% in March 2018, and then increased to 4% in June 2021. PLHIV newly initiated on ART increased by 60% from 0.5M in March 2016 to 0.8M in September 2017, before decreasing by 25% to 0.6M in June 2021.The proxy linkage to treatment rate increased from a low of 60% in March 2016 to approximately 90% in June 2021.

**Conclusion:** Countries substantially reduced the number of HIV tests conducted over the past three years, resulting in fewer HIV diagnoses but a stable percent positivity. Countries have also become more efficient in linking PLHIV identified to HIV treatment. To ensure continued progress towards 95-95-95 goals, HTS programs need to balance efforts to make testing more efficient (represented by percent positivity) without compromising the number of PLHIV diagnosed.




## 90 DETECTING RECENT HIV INFECTIONS IN OUTPATIENT DEPARTMENTS: A MULTI-COUNTRY ANALYSIS

**Suzue Saito**[1], Lenhle D. Nsibandze[2], Samkelo Simelane[3], Dumile Sibandze[2], Vusie Lokotfwako[2], Munyaradzi Pasipamire[4], Peter Fonjungo[5], Aime Mboyo[6], Tania L. Tchissambou[7], Mugyenyi Asiimwe[8], Appolinaire Tiam[9], Tlhomola Mphotleng[10], Keisha Jackson[4], Michael Martin[4], Stephanie Behel[4]

*[1]ICAP at Columbia University, New York, NY, USA, [2]Ministry of Health, Mbabane, Swaziland, [3]ICAP at Columbia University, Mbabane, Swaziland, [4]Centers for Disease Control and Prevention, Atlanta, GA, USA, [5]Centers for Disease Control and Prevention, Kinshasa, Congo, The Democratic Republic Of The, [6]Programme National de lutte contre le SIDA, Kinshasa, Congo, The Democratic Republic Of The, [7]ICAP at Columbia University, Kinshasa, Congo, The Democratic Republic Of The, [8]Centers for Disease Control and Prevention, Maseru, Lesotho, [9]Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, [10]Ministry of Health, Maseru, Lesotho*

**Background:** Diagnosing all persons living with HIV (PLHIV) as early as possible after infection is critical to reach and sustain HIV epidemic control. The U.S. President's Emergency Plan for AIDS Relief has prioritized index testing over testing in outpatient departments (OPD) as the most efficient means to locate PLHIV. HIV recent infection surveillance using recent infection testing algorithms (RITA) in routine HIV testing services (HTS) can help identify which testing approaches are effective at identifying PLHIV earlier to inform their public health response.

**Methods:** We analyzed data from 268 health facilities offering recency testing in the following locations and time-periods: Democratic Republic of Congo (DRC), November 2020–September 2021; Eswatini, July 2019–September 2021; and Lesotho, August 2019–April 2020. In DRC and Eswatini, RITA was used to identify recent cases defined as those newly diagnosed HTS clients ≥15 years (Eswatini) or ≥18 years (DRC) with a recent result on a rapid test for recent infection (RTRI) assay and a viral load of ≥1000 HIV RNA copies/mL. In Lesotho, we used RTRI assay results only in HTS clients ≥18 years. We examined the share and yield of RITA or RTRI recent cases by testing modality (see full list in table 1), stratified by age (<30, ≥30 years) and sex. We used Poisson regression to assess statistical significance for both measures.

**Results:** Of 18,170 (63% female) PLHIV with an RTRI result in the 3 countries, 4% were RITA recent in DRC, 5% were RITA recent in Eswatini, and 18% were RTRI recent in Lesotho. In all countries, OPD accounted for the largest share of newly diagnosed HIV cases identified; concomitantly OPD accounted for the largest share of recent infections. In Eswatini, VCT and index testing were additionally significantly associated with recent infections. This pattern remained in age/sex disaggregated analyses, with the exception of females <30 years in Eswatini for whom ANC/L&D/PNC/CWC clinics were additionally significantly associated with recent infections. Yield of recent infections were highest in FP and STI clinics in Eswatini, VCT clinics in DRC and ANC/L&D/PNC/CWC clinics in Lesotho. Testing volume was low in these modalities compared to OPD.

**Conclusion:** OPD is an effective testing approach to identify new infections. FP, STI, VCT, ANC/L&D/PNC/CWC had higher yield in some settings, suggesting that OPD could improve efficiency with more targeted testing. HIV recent infection surveillance can help inform testing interventions.

**Table 1. RTRI Tested and RITA Recent by Testing Modality by Country**

| | Eswatini | | | | | DRC | | | | | Lesotho | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RTRI Tests Administered (78% of Eligible Newly HIV+) | | RITA Recent | | RITA Recent for Females < 30 | | | RTRI Tests Administered (96% of Eligible Newly HIV+) | | RITA Recent | | | RTRI Tests Administered (71% of Eligible New HIV+) | | RTRI Recent | | |
| | n | % of Total | n | % Yield | % of Total | n | % of Total | n | % of Total | n | % Yield | % of Total | n | % of Total | n | % Yield | % of Total |
| *ART Clinic* | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | 11 | 1% | 0 | 0% | 0% |
| *Family Planning* | 139 | 1% | 18 | 13%*** | 3%*** | 18 | 4%** | N/A | N/A | N/A | N/A | N/A | NA | NA | NA | NA | NA |
| ***Index Testing*** | **3588** | **25%** | **151** | **4%** | **22%*** ** | **92** | **21%*** ** | 382 | 15% | 8 | 2% | 8% | NA | NA | NA | NA | NA |
| *Inpatient/TB* | 324 | 2% | 15 | 5% | 2%*** | 9 | 2%*** | 137 | 5% | 5 | 4%* | 5% | 5 | 0% | 0 | 0% | 0% |
| *ANC/L&D/PNC/CWC* | 1084 | 7% | 83 | 8%*** | 12%* | **76** | **17%** | 122 | 5% | 7 | 6%** | 7% | 41 | 4% | 11 | 27%$^{REF}$ | 5%$^{REF}$ |
| *Mobile/Community Outreach* | 1740 | 12% | 57 | 3%$^{REF}$ | 8%$^{REF}$ | 38 | 9%$^{REF}$ | 651 | 26% | 6 | 1%$^{REF}$ | 6%$^{REF}$ | 1 | 0% | 0 | 0% | 0% |
| ***OPD/Emergency*** | **4632** | **32%** | **171** | **4%** | **26%*** ** | **106** | **24%*** ** | **1013** | **40%** | **66** | **7%*** ** | **65%*** ** | **949** | **85%** | **187** | **20%** | **91%*** ** |
| *STI Clinic* | 97 | 1% | 12 | 12%*** | 2%*** | 7 | 2%*** | N/A | N/A | N/A | N/A | N/A | NA | NA | NA | NA | NA |
| ***VCT*** | **2692** | **19%** | **159** | **6%*** ** | **24%*** ** | **101** | **23%*** ** | 57 | 2% | 6 | 11%*** | 6% | NA | NA | NA | NA | NA |
| *VMMC* | 140 | 1% | 6 | 4% | 1%*** | 0 | 0% | N/A | N/A | N/A | N/A | N/A | NA | NA | NA | NA | NA |
| *Other/Missing/NR* | 104 | 1% | 3 | 3% | 0%*** | 1 | 0%*** | 150 | 6% | 3 | 2% | 3% | 111 | 10% | 8 | 7%** | 4% |
| Total by Country | 14540 | 100% | 675 | 5% | 100% | 447 | 100% | 2512 | 100% | 101 | 4% | 100% | 1118 | 100% | 206 | 18% | 100% |

% Yield: RITA recent/RITA Recent + RITA LT; % of Total: RITA recent for specific modality/total RITA recent. ART = antiretroviral treatment, FP = family planning, TB = tuberculosis clinic, ANC = antenatal care,L&D = labor and delivery, PNC = post-natal clinic, CWC = child welfare clinic, OPD = outpatient department/emergency, STI = sexually transmitted infection clinic, VCT = voluntary counselling and testing, VMMC = voluntary medical male circumcision, NR = not reported; * p < 0.05, ** p < 0.01, *** p < 0.001

## 91 HIV AND VIREMIA PREVALENCE IN NONMIGRATING MEMBERS OF MIGRANT HOUSEHOLDS IN UGANDA

New Investigator Scholar

**Ruth Young**[1], Joseph Ssekasanvu[1], Fred Nalugoda[2], Joseph Kagaayi[2], Robert Ssekubugu[2], Godfrey Kigozi[2], Steven J. Reynolds[3], Lisa J. Nelson[4], Maria Wawer[1], Bareng A. Nonyane[1], Larry W. Chang[5], Caitlin E. Kennedy[1], Ligia Paina[1], David Serwadda[6], M Kate Grabowski[5]

*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]Rakai Health Sciences Program, Kalisizo, Uganda, [3]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [4]Centers for Disease Control and Prevention, Kampala, Uganda, [5]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [6]Makerere University, Kampala, Uganda*

**Background:** Migration is associated with a higher risk of HIV acquisition and viremia among migrants, but less is known about the indirect effects of migration on non-migrating household members. Here, we evaluated whether non-migrating persons with migrant household members were more likely to be living with HIV and to be viremic compared to persons in households with no recent in or out-migration (non-migrant households).

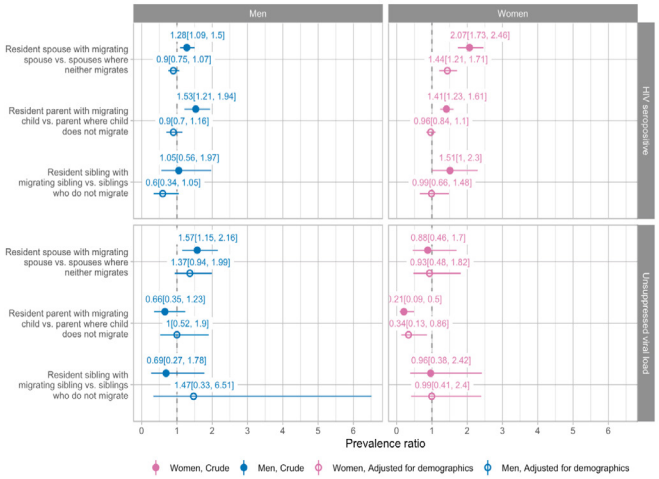
**Methods:** We used data from participants aged 15–49 years in the Rakai Community Cohort Study, a population-based census and survey in 41 communities in south-central Uganda. Data were collected during a single survey conducted between August 2016 and May 2018. Migrant households were those households reporting ≥1 member moving from another community into or out of the household with the intention to stay since the prior survey (~18 months) at census. HIV status was assessed with a validated rapid test algorithm, and viremia was defined as >1,000 viral copies/mL using the Abbott RealTime assay. Crude (cPR) and adjusted (adjPR) prevalence ratios with 95% confidence intervals (CI) were estimated using univariate and multivariate modified Poisson regressions adjusted for resident demographics, including age. Analyses were stratified by sex, the direction of migration (i.e., into or out of the household), and the relationship between non-migrant residents and migrants (i.e., spouse, child, sibling).

**Results:** There were 14,599 non-migrant participants (7,654 women; 6,945 men) in 9,299 households. Of these, 4,415 (30%) participants lived in a household with a recent in- or out-migrant, of whom 22% (n=972) had a migrant spouse, 25% (n=1,102) a migrating child/children, and 20% (n=875) a migrating sibling(s). Overall, HIV prevalence and viremia did not differ between non-migrant participants in migrant and non-migrant households. However, in analyses stratified by sex and relationship to migrant (Figure 1), women with migrant spouses were more likely to be living with HIV compared to women with non-migrant spouses (adjPR:1.44 [1.21-1.71]), and men with migrant spouses were more likely to be viremic (cPR:1.57 [1.15-2.16]; adjPR:1.37 [0.94-1.99]). Mothers with migrant children were less likely to be viremic (adjPR:0.34 [0.13-0.86]).

**Conclusion:** Individuals with migrating spouses have a significantly higher HIV burden. Therefore, couple-centric sexual health interventions addressing

situations where one partner is a migrant could prevent HIV and encourage engagement in HIV care and treatment.

**Figure 1: Crude and adjusted prevalence ratios for HIV and unsuppressed HIV by relationship to migrants.**




Note: Prevalence ratios presented with 95% confidence intervals, spouse regressions adjusted for demographics except for marital status; parent and sibling regressions adjusted for demographics including marital status.

## 92 THE IMPACT OF FREE ANTIRETROVIRAL THERAPY FOR NONCITIZEN PREGNANT WOMEN IN BOTSWANA

New Investigator Scholar

**Christina Fennell**[1], Daniel J. Escudero[1], Rebecca Zash[2], Modiegi Diseko[3], Gloria Mayondi[3], Judith Mabuta[3], Tumalano Sekoto[3], Tendani Gaolathe[3], Mompati Mmalane[3], Shahin Lockman[4], Joseph Makhema[3], Roger L. Shapiro[1]
*[1]Harvard TH Chan School of Public Health, Boston, MA, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [4]Brigham and Women's Hospital, Boston, MA, USA*

**Background:** In December 2019, the Botswana government expanded free antiretroviral therapy (ART) to include non-citizens. We evaluated the impact of this policy expansion on antenatal care, ART coverage, and adverse birth outcomes.

**Methods:** The Tsepamo surveillance study collects data at up to 18 delivery sites in Botswana. We compared outcomes in citizens and non-citizens living with HIV before and after the December 2019 ART expansion to non-citizens. We used chi-square, Fisher's exact, and Wilcoxon-Rank sum tests to compare antenatal visits, ART use in pregnancy, and the following birth outcomes: preterm delivery (PTD) <37 weeks, very preterm delivery (VPTD) <32 weeks, small for gestational age (SGA) <10th percentile, very small for gestational age (VSGA) <3rd percentile, stillbirth, and neonatal death. Log-binomial regression models were constructed to generate adjusted risk ratios (aRR).

**Results:** From August 2014 to September 2021, 46,238 (96.8%) citizens and 1,533 (3.2%) non-citizens living with HIV delivered at Tsepamo sites; 955 (62.3%) non-citizen deliveries were before the ART expansion (pre-expansion), and 578 (37.7%) were after (post-expansion). Post- expansion, non-citizen attendance at antenatal care increased (87.5% vs.79.3%, p<0.0001), narrowing the gap with citizens (96.3% in post-expansion period). Non-citizens became more likely to receive any antenatal ART (89.3% vs. 65.5%, p<0.0001), closer to ART use among citizens (96.9% in post-expansion period). Use of dolutegravir (DTG)-based ART increased post-expansion in non-citizens (42.7% vs. 6.7%, p<0.0001), as in citizens (44.6% vs 21.5%, p<0.0001). Compared with citizens, non-citizens living with HIV in the pre-expansion period had greater risk of PTD, VPTD, and neonatal death, but reduced risk of SGA (Table). Post-expansion, greater declines in most adverse outcomes were observed in non-citizens compared with citizens, and although power was limited, none of the adverse birth outcomes remained significantly associated with non-citizenship (Table). These trends in improved birth outcomes were not apparent among women without HIV (data not shown).

**Conclusion:** Following the expansion of free ART to non-citizens in Botswana, gaps narrowed in antenatal care and ART use in pregnancy between citizens and non-citizens living with HIV. Prior disparities in adverse birth outcomes were no longer observed following the expansion of free DTG-based ART to non-citizens.

**Adverse birth outcomes in Botswana among citizens and non-citizens living with HIV, before and after ART expansion to non-citizens in December 2019**

| | August 2014 - November 2019 | | | December 2019 – September 2021 | | |
|---|---|---|---|---|---|---|
| | Citizen n = 33,024 (%) | Non-Citizen n = 955 (%) | aRR*, 95% CI | Citizen n = 13,214 (%) | Non-Citizen n = 578 (%) | aRR*, 95% CI |
| PTD | 6,626 (20.1) | 226 (23.7) | 1.28 (1.12, 1.45) | 2,259 (17.1) | 83 (14.4) | 0.85 (0.67, 1.06) |
| Very PTD | 1,547 (4.7) | 72 (7.5) | 1.79 (1.36, 2.30) | 492 (3.7) | 18 (3.1) | 0.58 (0.30, 1.01) |
| SGA | 6,534(19.8) | 140 (14.7) | 0.77 (0.65, 0.90) | 2,218 (16.8) | 88 (15.2) | 0.97 (0.78, 1.18) |
| Very SGA | 2,658 (8.0) | 57 (6.0) | 0.81 (0.61, 1.04) | 885 (6.7) | 37 (6.4) | 0.97 (0.67, 1.34) |
| Stillbirth | 954 (2.9) | 42 (4.4) | 1.41 (0.98, 1.95) | 373 (2.8) | 15 (2.6) | 0.69 (0.34, 1.22) |
| Neonatal Death | 527 (1.6) | 27 (2.8) | 1.73 (1.07, 2.62) | 176 (1.3) | 11 (1.9) | 1.30 (0.61, 2.43) |

*Adjusted for maternal age, education, occupation, marital status, and parity.

## 93 DO INCENTIVE VOUCHERS IMPROVE HIV TREATMENT OUTCOMES AMONG KEY POPULATIONS IN INDIA?

**Sunil S. Solomon**[1], Allison M. McFall[1], Aylur K. Srikrishnan[2], Vasudevan C. Kesavan[2], Rifa Khan[2], Anand Santhanam[2], Saravanan Shanmugam[2], Paneerselvam Nandagopal[2], David C. Celentano[1], Shruti H. Mehta[1], Gregory M. Lucas[1]
*[1]The Johns Hopkins University, Baltimore, MD, USA, [2]YR Gaitonde Center for AIDS Research and Education, Chennai, India*

**Background:** Incentives have been evaluated as a means to improve HIV treatment outcomes in several settings. However, little work has focused on key populations in low and middle income countries.

**Methods:** We used a matched-pair cluster-randomized trial to compare incentives with usual care in 16 sites (8 PWID and 8 MSM) across India. At each site, we followed ~150 HIV-positive PWID/MSM participants who had <12 months or no prior exposure to antiretroviral therapy (ART). We implemented the trial from key population-focused integrated care centers. Government ART centres provided free ART. At incentive sites, participants received vouchers redeemable for food or goods for i) visiting ART centres prior to ART initiation, 2) initiating ART, 3) collecting timely ART refills, and 4) participating in quarterly motivational interviewing sessions. We quantified HIV RNA semi-annually from stored specimens and abstracted refill data from ART centre records. The primary outcome was survival with HIV RNA suppression (<150 c/mL) at month 12. Secondary outcomes included medication possession ratio (MPR), days in possession of ART divided by total follow-up days. We used a 2-stage cluster-level analysis for matched pairs to adjust for baseline viral suppression.

**Results:** We recruited 1,200 PWID and 1,114 MSM participants from Oct 2017-Oct 2018. The site median (range) age and monthly income were 30 years (26, 38) and USD 86 (0, 143), respectively. Across the 8 incentive sites, 95% of participants earned ≥1 incentive (site range: 78, 99) and the median earning through 12 months was USD 23 (site range: 3, 29). Survival with viral suppression was not significantly different in the incentive and usual care arms: crude prevalence 48% vs. 35%, respectively (adjusted prevalence ratio [aPR]: 1.22; 95% CI: 0.63, 2.34) (Table). The percent with MPR ≥90% were not significantly different in the incentive and usual care arms: crude prevalence 65% and 46%, respectively (aPR: 1.37; 95% CI: 0.77, 2.46). In stratified analyses, the effect size was similar in the 2 populations, although the effect was statistically significant among MSM but not among PWID. There were 57 and 83 deaths in the incentive and usual care arms, respectively.

**Conclusion:** In this large cluster-randomized trial, HIV treatment incentives were not significantly associated with increased ART use or survival with viral suppression at 12 months. Overall, treatment outcomes were poor and mortality high among these vulnerable populations.

**Table. Primary and secondary outcomes of trial comparing HIV treatment incentives to usual care**

| Outcome | | Adjusted prevalence ratio (95% CI) [Incentives vs. usual care] | | |
|---|---|---|---|---|
| | | Overall | PWID | MSM |
| Primary | Survival with viral suppression at 12 months | 1.22 (0.63, 2.34) | 1.52 (0.26, 8.74) | 0.97 (0.65, 1.43) |
| Secondary | ART medication possession ratio ≥ 90% | 1.37 (0.77, 2.46) | 1.72 (0.31, 8.19) | 1.22 (1.11, 1.34) |

## 94 THE COOPERATIVE RE-ENGAGEMENT CONTROLLED TRIAL: DURABLE VIRAL SUPPRESSION ASSESSMENT

**Jesse O'Shea**[1], Robyn Fanfair[1], George Khalil[1], Tiffany Williams[2], Kathleen Brady[3], Alfred DeMaria[4], Heidi Jenkins[5], Liisa Randall[4], Nasima Camp[2], Crystal Lucas[3], Marianne Buchelli[5], Taraz Samandari[1], Paul Weidle[1]
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]Social & Scientific Systems, Silver Spring, MD, USA, [3]Philadelphia Department of Public Health, Philadelphia, PA, USA, [4]Massachusetts Department of Public Health, Boston, MA, USA, [5]Connecticut Department of Public Health, Hartford, CT, USA*

**Background:** Retention in care and durable viral suppression (DVS) are associated with improved HIV clinical outcomes among persons with HIV (PWH). Health departments and clinics implemented a collaborative data-to-care strategy to identify persons newly out-of-care and an active public health intervention with goals of increasing re-engagement in care and increasing durable viral suppression.
**Methods:** A multi-site, prospective randomized trial was conducted to evaluate differences in HIV care continuum outcomes between participants randomized to receive an active public health intervention or standard of care (SOC). Newly out-of-care participants were identified using surveillance and clinic data in Connecticut (CT), Massachusetts (MA) and Philadelphia (PHL). Durable viral load suppression was defined as 2 consecutive suppressed viral load results (<200 copies/mL) at least 3 months apart within 18 months of randomization. Time to DVS was defined as time from randomization to the second of the two suppressed viral loads. Rank Sum Tests were used to compare median days to DVS and logistic regression models to assess DVS relationships.
**Results:** Between August 2016 and July 2018, 1893 participants were randomized from CT (n=654), MA (n=630), and PHL (n=609). Rates of achieving DVS comparing intervention to SOC across all sites were 437 (45.6%) vs 416 (44.5%), p=0.62; CT: 162 (48.8%) vs 149 (46.3%), p=0.52; MA:136 (42.9%) vs 147 (47%), p=0.31; PHL: 139 (45%) vs 120 (40%), p=0.21. When controlling for age, race, sex, exposure category, and CD4 count, the odds of achieving DVS varied by site, but we could not exclude the null of no difference between study groups. The median time, days (IQR, n), to DVS after randomization comparing intervention vs SOC were: All sites: 280 days (204-381, n=437) vs 300 days (217-400, n=416); p=0.05, CT: 289 days (210-392, n=162) vs 308 days (218-393, n=149); p=0.56, MA: 295 days (220.5-390.5, n=136) vs 286 days (203-401, n=147); p=0.70, PHL: 246 (180-358, n=139) vs 289.5 (218-403.5, n=120); p=0.001.
**Conclusion:** This trial showed that a collaborative, data-to-care strategy, and active public health intervention did not increase the proportion of PWH achieving durable viral suppression but may reduce the time to achieving DVS.

## 95 CAB-LA PrEP: EARLY DETECTION OF HIV INFECTION MAY REDUCE InSTI RESISTANCE RISK




**Susan Eshleman**[1], Jessica M. Fogel[1], Elias K. Halvas[2], John W. Mellors[2], Estelle M. Piwowar-Manning[1], Alex R. Rinehart[3], Marybeth McCauley[4], Adeola Adeyeye[5], Juan C. Hinojosa[6], Robinson Cabello[7], Keren Middelkoop[8], Myron S. Cohen[9], Beatriz Grinsztejn[10], Raphael J. Landovitz[11]
*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]ViiV Healthcare, Research Triangle Park, NC, USA, [4]FHI 360, Durham, NC, USA, [5]National Institutes of Health, Bethesda, MD, USA, [6]Asociación Civil Selva Amazónica, Iquitos, Peru, [7]Asociación Via Libre, Lima, Peru, [8]University of Cape Town, Cape Town, South Africa, [9]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [10]Instituto de Pesquisa Clinica Evandro Chagas-Fiocruz, Rio de Janeiro, Brazil, [11]University of California Los Angeles, Los Angeles, CA, USA*

**Background:** HPTN 083 and 084 demonstrated that long-acting injectable cabotegravir (CAB-LA) is highly effective for HIV prevention; rare breakthrough infections were observed. Detection of HIV infection in participants who received CAB PrEP was often delayed using standard HIV testing algorithms. In HPTN 083, integrase strand transfer inhibitor (InSTI) resistance-associated mutations (RAMs) were detected in 5 CAB-exposed participants with HIV infection (GenoSure PRIME assay, viral load [VL] ≥500 c/mL); 2 other participants did not have genotyping results since all VLs were <500 c/mL. In all 7 participants, detection of infection at study sites using rapid tests and antigen/antibody tests was delayed (median 60 days; range 35-117) and all 7 participants received CAB-LA injections after infection occurred. We used a single-genome sequencing (SGS) InSTI genotyping assay to assess whether earlier detection of these HIV infections would have provided an opportunity to start antiretroviral treatment (ART) before InSTI resistance emerged.
**Methods:** SGS testing was performed for 21 samples from the 7 participants described above (1 baseline infection; 6 incident infections). The 21 samples tested positive with Aptima HIV-1 RNA Qualitative Assay result (limit of detection [LOD]: 30 c/mL) and had VLs <500 c/mL. The Stanford HIV Drug Resistance Database was used for InSTI RAMs.
**Results:** The SGS assay was successful for 18/21 samples tested. The assay detected InSTI RAMs in 6/7 participants (4/5 with prior genotyping results, 2/2 with no prior genotyping results). Use of an RNA assay with an LOD of 30 copies/mL detected infection before a major InSTI RAM was detected (4 cases) or before additional major InSTI RAMs accumulated (2 cases). In the last case, this could not be assessed since SGS was not successful before the first site-positive visit.
**Conclusion:** Consistent with newly released CDC guidelines, earlier detection of HIV infection using an HIV RNA assay in the setting of CAB-LA PrEP would allow for earlier ART initiation which may reduce the risk of InSTI resistance. Given the low levels of viremia often seen in this setting, VL testing for HIV screening should be performed using the most sensitive assay available. In the context of proven high efficacy, CAB-LA should also be considered for HIV PrEP in settings where HIV RNA screening is not readily available.

## 96 UPDATED EFFICACY, SAFETY, AND CASE STUDIES IN HPTN 083: CAB-LA VS TDF/FTC FOR PrEP




**Raphael J. Landovitz**[1], Deborah Donnell[2], Ha Tran[3], Esper G. Kallas[4], Manya Magnus[5], Mark Marzinke[6], Susan Eshleman[6], Brett Hanscom[2], Adeola Adeyeye[7], James F. Rooney[8], Alex R. Rinehart[9], Myron S. Cohen[10], Marybeth McCauley[11], Beatriz Grinsztejn[12]
*[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]University of North Carolina in Vietnam, Hanoi, Vietnam, [4]University of Sao Paulo, Sao Paulo, Brazil, [5]George Washington University, Washington, DC, USA, [6]The Johns Hopkins University, Baltimore, MD, USA, [7]National Institutes of Health, Rockville, MD, USA, [8]Gilead Sciences, Inc, Foster City, CA, USA, [9]ViiV Healthcare, Research Triangle Park, NC, USA, [10]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [11]FHI 360, Washington, DC, USA, [12]Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil*

**Background:** HPTN 083 is an ongoing Phase IIb/III randomized controlled trial that demonstrated superior efficacy with 66% reduced risk of HIV acquisition for long-acting injectable cabotegravir (CAB-LA) vs. daily oral TDF/FTC in the prespecified primary analysis. After unblinding in May 2020, participants continued on their original randomized study treatment until the protocol was amended and operationalized to offer eligible participants open-label CAB-LA. Fifty-one incident HIV infections were identified in the blinded trial (12 CAB, 39 TDF/FTC).
**Methods:** We report updated HIV incidence rates in both study arms during the blinded phase of the trial (original primary analysis period) and for one year of follow-up. Two criteria were used for incident HIV infections: detection of infection by study sites before 8/15/21; and first HIV positive visit based on site and centralized testing before 5/15/21. The primary incidence analysis prespecified exclusion of infections that occurred ≥3 years after study enrollment. Safety data were updated to include events up to 5/15/21. Virology and pharmacology assays were used to characterize HIV infections.
**Results:** With this one year of additional follow-up, we identified 46 additional incident HIV infections in the pre-planned analysis period (13 CAB, 33 TDF/FTC); 4 occurred during the blinded phase (2 CAB, 2 TDF/FTC), 42 after unblinding (11 CAB, 31 TDF/FTC). Reduction in risk for CAB-LA vs. FTC/TDF remained similar in blinded and unblinded phases (HR=0.33 95%CI (0.18-0.62) and HR=0.34 95%CI (0.17-0.67), Table). HIV incidence was higher in both arms in the unblinded phase, likely attributable to decreased TDF/FTC adherence, reduced CAB injection coverage, and increased relative contributions to overall person-time from high incidence regions. No new safety concerns were identified. The 2 newly-identified blinded CAB arm infections were both in the setting of on-time injections; the 11 newly-identified unblinded CAB arm infections included 1 with on-time injections, 3 with delayed injections, and 7 that occurred ≥6 months after the last CAB exposure (2 of these 7 never received a CAB injection). Six additional new CAB arm infections were identified ≥3 years on study (all ≥6 months after the last CAB exposure).
**Conclusion:** The HRs for HIV incidence reduction for CAB-LA vs. oral TDF/FTC were consistent during one year of additional unblinded study follow-up. The

correlates of CAB PrEP breakthrough are under investigation. No new safety concerns were identified.

**Table.** HIV incidence and relative effectiveness of cabotegravir compared to TDF/FTC

| | CAB | TDF/FTC | HR (95% CI) |
|---|---|---|---|
| **UPDATED PRIMARY BLINDED PERIOD** | | | |
| **HIV incidence and relative effectiveness** | | | |
| Incident HIV infections, n | 14 | 41 | 0.34 (0.18, 0.62) |
| Accrued person-time, pyrs | 3204 | 3186 | |
| Incidence, events/100pyrs (95% CI) | 0.44 (0.24, 0.73) | 1.29 (0.92, 1.75) | |
| **Study product adherence** | | | |
| CAB injection person-years covered*, % | 2183 (91.5%) | | |
| Detectable plasma TFV samples, n (%) | | 1763 (86.0%) | |
| Plasma TFV concentration samples ≥ 40 ng/ml, n (%) | | 1522 (74.2%) | |
| DBS TFV–DP concentration samples ≥700 fmol/punch, n (%) | | 1472 (72.4%) | |
| **YEAR ONE UNBLINDED PERIOD** | | | |
| **HIV incidence and relative effectiveness** | | | |
| Incident HIV infections, n | 11 | 31 | 0.33 (0.17, 0.67) |
| Accrued person-time, pyrs | 1455 | 1410 | |
| Incidence, events/100pyrs (95% CI) | 0.76 (0.38, 1.35) | 2.20 (1.49, 3.12) | |
| **Study product adherence** | | | |
| CAB injection person-years covered*, % | 79.9% | | |
| Detectable plasma TFV samples, n (%) | | 369 (76.1%) | |
| Plasma TFV concentration samples ≥ 40 ng/ml, n (%) | | 308 (63.5%) | |
| DBS TFV–DP concentration samples ≥700 fmol/punch, n (%) | | 281 (59.4%) | |
| **ALL DATA COMBINED** | | | |
| **HIV incidence and relative effectiveness** | | | |
| Incident HIV infections, n | 25 | 72 | 0.34 (0.21, 0.54) |
| Accrued person-time, pyrs | 4660 | 4596 | |
| Incidence, events/100pyrs (95% CI) | 0.54 (0.35, 0.79) | 1.57 (1.23, 1.97) | |
| **Study product adherence** | | | |
| CAB injection person-years covered*, % | 87.9% | | |
| Detectable plasma TFV samples, n (%) | | 2141 (83.6%) | |
| Plasma TFV concentration samples ≥ 40 ng/ml, n (%) | | 1835 (71.7%) | |
| DBS TFV–DP concentration samples ≥700 fmol/punch, n (%) | | 1657 (66.4%) | |

*The initial injection is assumed to provide 6 weeks of coverage, and subsequent injections are assumed to provide 10 weeks of coverage. Any injection given more than 16 weeks after the prior injection is treated as an "initial dose" and assumed to provide 6 weeks of coverage.

TDF/FTC, tenofovir/emtricitabine; CAB, cabotegravir; CI, confidence interval; pyrs, person-years; TFV, tenofovir; DBS, dried blood spots; TFV–DP, tenofovir-diphosphate

## 97 SYMPTOM DURATION IN COVID-19 CONVALESCENT PATIENTS: REGIONAL & CLINICAL ASSOCIATIONS

**Jorge A. Gallardo-Cartagena**[1], Juan J. Montenegro-Idrogo[1], Sue Li[2], Jiani Hu[2], Abhishek B. Amin[2], Portia Hunidzarira[3], Paul Goepfert[4], Megan Jones[2], Vicky Kim[2], Robert De La Grecca[2], Azwi Takalani[2], Simbarashe Takuva[2], Lawrence Corey[2], Shelly Karuna[2]

*[1]Centro de Investigaciones Tecnológicas, Biomédicas y Medioambientales, Universidad Nacional Mayor de San Marcos, Lima, Peru, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC), Harare, Zimbabwe, [4]University of Alabama at Birmingham, Birmingham, AL, USA*

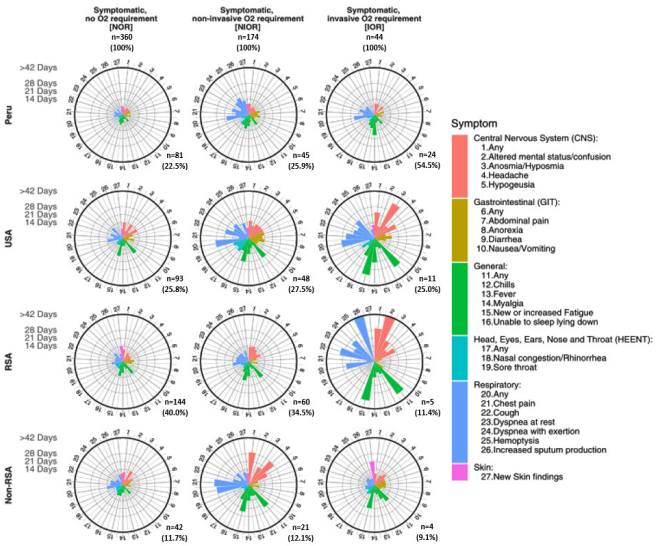
**Background:** Post-Acute Sequelae of SARS-CoV-2 (PASC) is characterized by persistent symptoms negatively impacting quality of life several weeks after SARS-CoV-2 diagnosis. Proposed risk factors include older age, female sex, comorbidities, and severe COVID-19, including hospitalization and oxygen requirement. Yet, associations of these factors with prolonged symptoms remain poorly understood globally.

**Methods:** The global, observational cohort study HVTN 405/HPTN 1901 characterizes the clinical and immunologic course in the first year after SARS-CoV-2 infection among adults. The cohort was categorized by infection severity (asymptomatic; symptomatic with no oxygen requirement [NOR]; non-invasive oxygen requirement [NIOR]; or invasive oxygen requirement [IOR]). A regression model was applied to estimate geometric mean ratios (GMR) for duration and odds ratios (OR) for persistence of symptoms.

**Results:** 759 participants from Peru (25.2%), USA (26.0%), Republic of South Africa (RSA, 37.7%), and non-RSA Sub-Saharan Africa (11.2%) were enrolled a median of 51 (IQR 35-66) days post-diagnosis, from May 2020 to Mar 2021. 53.8% were female, 69.8% were <55yo (median 44yo, IQR 33-58) and identified as non-Hispanic Black (42.7%), Hispanic (27.9%) or non-Hispanic White (15.8%). Comorbidities included obesity (42.8%), hypertension (24%), diabetes (14%), HIV infection (11.6%) and lung disease (7.5%). 76.2% were symptomatic (NOR 47.4%; NIOR 22.9%; and IOR 5.8%). Among symptomatic participants, median acute COVID-19 duration was 20 days (IQR 11-35); 43.3% had ≥1 persistent symptom after COVID-19 resolution (39.8% NOR; 49.1 % NIOR+IOR; p=0.037); 16.8% reported ≥1 symptom >42 days (14.0% NOR; 21.6% NIOR+IOR; p=0.025). Symptom duration was not associated with age or sex assigned at birth but was associated with disease severity (GMR 2.09; 95%CI 1.5-2.91, p<0.001 for NIOR vs NOR; not significant for IOR vs NIOR), lung disease (GMR 2.43; 95%CI 1.42-4.16, p=0.001), and global region (p<0.05, see Figure 1). Prolonged viral shedding was associated with persistent diarrhea (OR 6.59; 95%CI 1.65 – 26.86; p=0.008).

**Conclusion:** A recovery course consistent with PASC was significantly associated with infection severity, lung disease, and region. Regional differences in symptom profiles and duration may be influenced by viral diversity, genetic, or cultural factors and likely reflect disparities in healthcare access and interventions. Better understanding PASC associations may improve clinical assessment and management globally.

**Figure 1: Polar-plot of median COVID-19 symptom duration by system, infection severity and region in the HVTN 405/HPTN 1901 cohort**




## 98 POST-ACUTE SEQUELAE OF SARS-CoV-2: CLINICAL CONDITION COMPARISON IN A MATCHED COHORT

**Michael A. Horberg**[1], Eric S. Watson[1], Celeena R. Jefferson[1], Julia M. Certa[1], Keri N. Althoff[2], Carolyn F. Williams[3], Richard Moore[2]

*[1]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA*

**Background:** Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) is a novel condition generally defined as new onset or persistence of symptoms related to SARS-CoV-2 beyond convalescence or first 30 days post-diagnosis. PASC has not been well defined by conditions or timeline manifestation. We measured PASC incidence in an integrated health system population (Kaiser Permanente Mid-Atlantic States; KPMAS) and provided supporting evidence for PASC-related conditions of focus (COF) identified from our previous research. Importantly, KPMAS is a closed healthcare system with high ascertainment of COVID-19 among our members, as well as PASC conditions and symptoms.

**Methods:** Using KPMAS electronic health records, we identified adult patients (≥18 years) who had a SARS-CoV-2 RT-PCR test result (detected or undetected) from 1/1/2020 to 12/31/2020. We defined 3 diagnostic time intervals, predicated on the first test date of identified PASC phenotypes. These time intervals were defined as: T1) "Prevalent": 4 years prior to PCR test identifying prevalent conditions; T2) "Acute/Persistent": 0-30 days post-PCR and persisted in 30-120 day follow-up; T3) "Incident/Late": 30-120 days post-PCR identifying incident conditions/symptoms. We enforced mutual exclusivity per patient by removing conditions and symptoms from T2 previously identified in T1 and those from T3 previously identified in T1 or T2. Diagnoses were grouped using Clinical Classification Software (CCS). The PCR-positive patients (cases) were matched to PCR-negative patients (controls) by month of test, age group, race, sex, and medical center. We prioritized 1:3 (case:control) matching, followed by 1:2, then 1:1. Risk ratios with 95% confidence intervals comparing case to control COF were calculated to determine significant COF.

**Results:** Matching successfully resulted in 28,118 cases and 70,293 controls. Demographic differences were negligible and showed no association (Highest Cramer's V: Age - .0511). Overall, risk of COF was 12% greater among cases than controls (Table 1). During T3, risk was significantly higher among cases for the following COF: anosmia, cardiac dysrhythmia, diabetes, genitourinary disorders, malaise, and nonspecific chest pain.

**Conclusion:** We delineated significant COF among those experiencing incident PASC in our KPMAS population. Our findings contribute to the overall evaluation of PASC and provide supporting evidence for an accepted definition. Further understanding the severity and duration of these conditions will be crucial.

**Table 1. Conditions of Focus Comparing Case and Controls During Time Intervals T3 and T2**

| | Time Interval | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incident - 30-120 Days Post COVID Test Period (T3) | | | | | Persistent - 0-30 Days Post-COVID 19 Test Period (T2) | | | | |
| CCS Category | Case (N) | Case Cumulative Incidence | Control (N) | Control Cumulative Incidence | Risk Ratio [95% CI] | Case (N) | Case Cumulative Incidence | Control (N) | Control Cumulative Incidence | Risk Ratio [95% CI] |
| Abdominal pain | 498 | 1.8% | 1182 | 1.7% | 1.05 [0.95,1.17] | 49 | 0.2% | 141 | 0.2% | 0.87 [0.63,1.20] |
| Anosmia | 90 | 0.3% | 58 | 0.1% | 3.88 [2.79,5.40]* | 2 | 0.0% | 10 | 0.0% | 0.50 [0.11,2.28] |
| Anxietydisorders | 323 | 1.1% | 799 | 1.1% | 1.01 [0.89,1.15] | 65 | 0.2% | 196 | 0.3% | 0.83 [0.63,1.10] |
| Cardiac dysrhythmias | 263 | 0.9% | 527 | 0.7% | 1.25 [1.08,1.45]* | 92 | 0.3% | 121 | 0.2% | 1.90 [1.45,2.49]* |
| Conditions associated with dizziness or vertigo | 478 | 1.7% | 1142 | 1.6% | 1.05 [0.94,1.16] | 69 | 0.2% | 159 | 0.2% | 1.08 [0.82,1.44] |
| Diabetes | 265 | 0.9% | 554 | 0.8% | 1.20 [1.03,1.38]* | 97 | 0.3% | 124 | 0.2% | 1.96 [1.50,2.55]* |
| Fluid and electrolyte disorders | 114 | 0.4% | 389 | 0.6% | 0.73 [0.59,0.90]* | 62 | 0.2% | 79 | 0.1% | 1.96 [1.41,2.74]* |
| Gastrointestinal | 481 | 1.7% | 1197 | 1.7% | 1.00 [0.90,1.12] | 114 | 0.4% | 292 | 0.4% | 0.98 [0.79,1.21] |
| Genitourinary symptoms and ill-defined conditions | 414 | 1.5% | 857 | 1.2% | 1.21 [1.07,1.36]* | 32 | 0.1% | 70 | 0.1% | 1.14 [0.75,1.74] |
| Malaise and fatigue | 398 | 1.4% | 622 | 0.9% | 1.60 [1.41,1.81]* | 81 | 0.3% | 70 | 0.1% | 2.89 [2.10,3.98]* |
| Mental health | 313 | 1.1% | 825 | 1.2% | 0.95 [0.83,1.08] | 46 | 0.2% | 184 | 0.3% | 0.62 [0.45,0.86]* |
| Nausea and vomiting | 191 | 0.7% | 503 | 0.7% | 0.95 [0.80,1.12] | 21 | 0.1% | 65 | 0.1% | 0.81 [0.49,1.32] |
| Nonspecific chest pain | 483 | 1.7% | 869 | 1.2% | 1.39 [1.24,1.55]* | 112 | 0.4% | 117 | 0.2% | 2.39 [1.85,3.10]* |
| Other lower respiratory disease | 315 | 1.1% | 860 | 1.2% | 0.92 [0.80,1.04] | 331 | 1.2% | 330 | 0.5% | 2.51 [2.15,2.92]* |
| Other nervous system disorders | 210 | 0.7% | 504 | 0.7% | 1.04 [0.89,1.22] | 30 | 0.1% | 77 | 0.1% | 0.97 [0.64,1.49] |
| Other nutritional; endocrine; and metabolic disorders | 136 | 0.5% | 298 | 0.4% | 1.14 [0.93,1.40] | 13 | 0.0% | 60 | 0.1% | 0.54 [0.30,0.99]* |
| Respiratoryfailure; insufficiency; arrest (adult) | 27 | 0.1% | 59 | 0.1% | 1.14 [0.73,1.80] | 202 | 0.7% | 22 | 0.0% | 22.95 [14.78,35.64]* |
| **Any condition** | **7350** | **26.1%** | **17709** | **25.2%** | **1.04 [1.01,1.07]*** | **5726** | **20.4%** | **15556** | **22.1%** | **0.92 [0.89,0.95]*** |
| **Conditions of Focus** | **3820** | **13.6%** | **8540** | **12.1%** | **1.12 [1.08,1.16]*** | **1139** | **4.1%** | **1782** | **2.5%** | **1.60 [1.48,1.72]*** |

1. Conditions of focus (COF) were identified by highest condition distributions in the specific time intervals and validated by infectious disease physicians
2. *Asterisk indicates significant result

## 99 INFLAMMATION, EXERCISE CAPACITY, CHRONOTROPY, AND SYMPTOMS IN POST-ACUTE COVID-19

Late Breaking

**Matthew S. Durstenfeld**[1], Michael J. Peluso[1], Punita Kaveti[1], Christopher Hill[1], Danny Li[1], Erica Sander[1], Shreya Swaminathan[1], Victor M. Arechiga[1], Victor Zepeda[1], Yoojin Lee[1], Mandar Aras[1], Donald J. Grandis[1], Carlin S. Long[1], Steven G. Deeks[1], Priscilla Hsue[1]

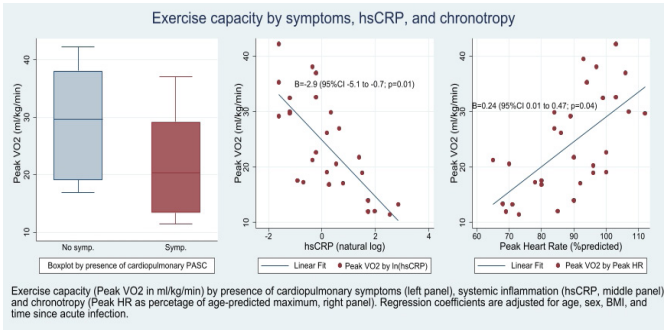
*[1]University of California San Francisco, San Francisco, CA, USA*

Background: Cardiopulmonary symptoms and reduced exercise capacity can persist after SARS-CoV-2 infection. Mechanisms of post-acute sequelae of COVID-19 ("PASC" or "Long COVID") remain poorly understood. We hypothesized that systemic inflammation would be associated with reduced exercise capacity and pericardial/myocardial inflammation.

**Methods:** As part of a COVID recovery cohort (NCT04362150) we assessed symptoms, biomarkers, and echocardiograms in adults >2 months after PCR-confirmed SARS-CoV-2 infection. In a subset, we performed cardiac magnetic resonance imaging (CMR), ambulatory rhythm monitoring (RM), and cardiopulmonary exercise testing (CPET) >12 months after acute infection. Associations between symptoms and oxygen consumption (VO2), cardiopulmonary parameters and biomarkers were evaluated using linear and logistic regression with adjustment for age, sex, BMI, and time since infection.

**Results:** We studied 120 participants (median age 51, 42% female, and 47% had cardiopulmonary symptoms at median 7 months after acute infection). Elevated hsCRP was associated with symptoms (OR 1.32 per doubling, 95%CI 1.01-1.73, p=0.04). No differences in echocardiographic indices were found except for presence of pericardial effusions among those with symptoms (p=0.04). Of the subset (n=33) who underwent CMR at a median 17 months, all had normal cardiac function (LVEF 53-76%), 9 (27%) had pericardial effusions and none had findings suggestive of prior myocarditis. There were no differences on RM by symptoms. On CPET, 33% had reduced exercise capacity (peak VO2 <85% predicted). Individuals with symptoms had lower peak VO2 compared to those reporting recovery (28.4 vs 21.4 ml/kg/min, p=0.04, Figure). Elevated hsCRP was independently associated with lower peak VO2 after adjustment (-9.8 ml/kg/min per doubling, 95%CI -17.0 to -2.5; p=0.01, Figure). The predominant mechanism of reduced peak VO2 was chronotropic incompetence (HR 19% lower than predicted, 95%CI 11-26%; p<0.0001, Figure). Chronotropic incompetence on CPET correlated with lower peak HR during ambulatory RM (p<0.001).

**Conclusion:** Persistent systemic inflammation (hsCRP) is associated with pericardial effusions and reduced exercise capacity > 1 year after acute SARS-CoV-2 infection. This finding appears to be driven mainly by chronotropic incompetence rather than respiratory compromise, cardiac pump dysfunction, or deconditioning. Evaluation of therapeutic strategies to target inflammation and/or chronotropy to alleviate PASC is urgently needed.




Exercise capacity (Peak VO2 in ml/kg/min) by presence of cardiopulmonary symptoms (left panel), systemic inflammation (hsCRP, middle panel) and chronotropy (Peak HR as percetage of age-predicted maximum, right panel). Regression coefficients are adjusted for age, sex, BMI, and time since acute infection.

## 100 SALIVA, NASAL & TEAR PK OF EIDD-1931 IN PATIENTS WITH COVID-19 RECEIVING MOLNUPIRAVIR

**Richard FitzGerald**[1], Laura Dickinson[2], Laura Else[2], Thomas Fletcher[3], Colin Hale[1], Alieu Amara[2], Lauren Walker[1], Sujan D. Penchala[2], Rebecca Lyon[1], Victoria Shaw[2], Helen Reynolds[2], Wendy P. Painter[4], Sean Ewings[5], Gareth Griffiths[5], Saye Khoo[2]

*[1]Liverpool University Hospital NHS Foundation Trust, Liverpool, UK, [2]University of Liverpool, Liverpool, UK, [3]Liverpool School of Tropical Medicine, Liverpool, UK, [4]Ridgeback Biotherapeutics, Miami, FL, USA, [5]Southampton Clinical Trials Unit, Southampton, UK*

**Background:** Molnupiravir, a prodrug of the broadly active, direct-acting antiviral, ribonucleoside analogue EIDD-1931, is a promising COVID-19 drug. Given the primary route of SARS-CoV-2 transmission through respiratory droplets we evaluated EIDD-1931 PK in saliva, nasal secretions and tears of patients with mild-to-moderate COVID-19 through the phase Ib/IIa AGILE platform (NCT04746183).

**Methods:** Patients with PCR-confirmed SARS-CoV-2 infection, within 5 days of symptom onset with mild-to-moderate disease were randomised to oral molnupiravir 300, 600 or 800 mg twice daily. Plasma and non-plasma (saliva, nasal and tear swabs) samples were collected pre-dose, 0.5, 1, 2, and 4 hours post-dose on study days 1 and 5 and molnupiravir and EIDD-1931 measured by LC/MS (lower limit of quantification, 2.5 ng/mL). PK parameters were determined (Phoenix 64, WinNonlin, v. 8.3) and non-plasma:plasma (NP:P) ratios (based on AUC0-4) calculated. Relationships between paired non-plasma and plasma samples were evaluated by linear regression.

**Results:** Twelve participants (n=4 per dose; 75% female) completed the study contributing 111, 112 and 97 saliva, nasal and tear samples, respectively. Molnupiravir was detected in 11% of saliva samples [median (range) 4.86 ng/mL (2.63-31.44)] and not evaluated in swabs. Quantifiable EIDD-1931, following molnupiravir 300, 600 and 800 mg twice daily were i) saliva: 17.7 (2.8-133), 16.6 (2.9-469), 25.8 (4.0-230) ng/mL, ii) nasal swabs: 182 (18-1700), 136 (18-917), 295 (24-1879) ng/mL and iii) tears: 297 (24-1650), 176 (16-1260), 307 (32-2760) ng/mL. PK parameters are shown (Table 1). Median (range, CV%) pooled NP:P ratio for saliva was 0.03 (0.01-0.11, 60%; n=16). Nasal and tear ratios were 6-fold higher with values of 0.21 (0.05-0.73, 70%; n=17) and 0.22 (0.09-1.05, 92%; n=12), respectively. Non-plasma and plasma concentrations were significantly correlated (r2: 0.360-0.677; p<0.0001). Of measured saliva, nasal and tear samples, 6, 50 and 61%, respectively were within or above the EIDD-1931 $EC_{90}$ against SARS-CoV-2 in primary human airway epithelia cultures (approximately 0.5-1 μM ≈ 130-260 ng/mL).

**Conclusion:** This is the first report of EIDD-1931 PK at sites of initial SARS-CoV-2 exposure in patients with COVID-19. Investigations of PK/PD relationships are warranted; however, these data suggest therapeutic concentrations are potentially achieved in nasal and tear compartments, but not saliva and have important implications for prophylactic coverage.

**Table 1** Geometric mean (CV%) EIDD-1931 PK parameters from plasma, saliva, nasal swabs and tear strips of SARS-CoV-2 infected patients following single (Day 1) and multiple dose (Day 5) molnupiravir 300 mg, 600 mg and 800 mg twice daily (n=4 per dosing arm unless stated otherwise).

| | 300 mg | | 600 mg | | 800 mg | |
|---|---|---|---|---|---|---|
| **Parameter** | **Day 1** | **Day 5** | **Day 1** | **Day 5** | **Day 1** | **Day 5** |
| ***Plasma*** | | | | | | |
| $AUC_{0\text{-}t}$ (ng.h/mL) | 3031 (45)* | 2328§ | 5690 (22)* | 4368 (41) | 8187 (30) | 7005 (21)* |
| $C_{max}$ (ng/mL) | 1488 (31)* | 1048 (17)* | 2440 (17) | 1865 (61) | 3447 (32) | 3546 (13)* |
| $T_{max}$ (h) | 2.00 (1.00-2.00)* | 1.00 (1.00-1.00)* | 1.00 (1.00-2.00) | 1.00 (1.00-2.00) | 2.00 (2.00-2.00) | 2.00 (2.00-2.00)* |
| $R_{AC}$ | NA | NC | NA | 0.91 (7)* | NA | 0.93 (20)* |
| ***Saliva*** | | | | | | |
| $AUC_{0\text{-}t}$ (ng.h/mL) | 65 (109)* | 106 (93)* | 143 (120) | 106 (77)* | 289 (52) | 237 (36)* |
| $C_{max}$ (ng/mL) | 29 (113)* | 41 (98) | 73 (127) | 48 (76)* | 134 (48) | 109 (27)* |
| $T_{max}$ (h) | 1.00 (1.00-2.00)* | 1.50 (1.00-2.00) | 2.00 (1.00-2.00) | 2.00 (2.00-4.00)* | 2.00 (1.00-2.00) | 2.00 (2.00-2.00)* |
| $R_{AC}$ | NA | 1.62 (31)* | NA | 0.59 (58)* | NA | 1.00 (13)* |
| $R_{NP:P}$ | 0.03 (62)# | 0.03§ | 0.04 (79)* | 0.03 (51)* | 0.04 (33) | 0.03 (18)* |
| ***Nasal Swabs*** | | | | | | |
| $AUC_{0\text{-}t}$ (ng.h/mL) | 1061 (38)* | 673 (27)* | 629 (64) | 716 (67) | 2164 (50) | 1611 (73)* |
| $C_{max}$ (ng/mL) | 905 (70)* | 484 (60) | 365 (75) | 321 (65) | 1076 (43) | 738 (87)* |
| $T_{max}$ (h) | 1.00 (1.00-1.00)* | 1.00 (1.00-2.00) | 1.00 (1.00-2.00) | 1.00 (1.00-4.00) | 1.50 (1.00-2.00) | 2.00 (2.00-4.00)* |
| $R_{AC}$ | NA | 0.63 (39)* | NA | 0.58 (47)* | NA | 0.90 (30)* |
| $R_{NP:P}$ | 0.41 (73)# | 0.23§ | 0.17 (27)* | 0.17 (112) | 0.26 (26) | 0.23 (67)* |
| ***Tear Strips*** | | | | | | |
| $AUC_{0\text{-}t}$ (ng.h/mL) | 1731 (44)* | 1071 (38)* | 1137 (96)* | 749 (50)# | 1934 (90)* | 722§ |
| $C_{max}$ (ng/mL) | 908 (58)* | 674 (53)* | 411 (100)* | 508 (84) | 985 (95)* | 1267 (40)* |
| $T_{max}$ (h) | 0.50 (0.50-2.00)* | 1.00 (0.50-2.00)* | 2.00 (0.50-4.00)* | 1.50 (1.00-2.00)# | 1.00 (1.00-1.00)* | 1.00 (0.50-1.00)* |
| $R_{AC}$ | NA | 0.62 (43)* | NA | 1.12 (85)# | NA | 0.80§ |
| $R_{NP:P}$ | 0.77 (36)# | 0.39§ | 0.20 (76)* | 0.17 (47)# | 0.26 (121)* | 0.10§ |

$T_{max}$ expressed as median (range)
* n=3, # n=2, § n=1
NA: not applicable; NC: not calculated due to missing samples on Day 1 or 5 preventing calculation of $AUC_{0\text{-}t}$; $AUC_{0\text{-}t}$: area under the concentration-time curve over 0 hours (pre-dose) to 4 hours post-dose; $C_{max}$: maximum concentration; $T_{max}$: time of maximum concentration; $R_{AC}$: accumulation ratio from day 1 to day 5 (Day 5 $AUC_{0\text{-}t}$/Day 1 $AUC_{0\text{-}t}$); $R_{NP:P}$: intercompartmental ratio of non-plasma to plasma (non-plasma $AUC_{0\text{-}t}$/plasma $AUC_{0\text{-}t}$)

## 101 PHASE III TRIAL OF MOLNUPIRAVIR IN ADULTS WITH MILD SARS-CoV-2 INFECTION IN INDIA

**Nagalingeswaran Kumarasamy**[1], Bibhuti Saha[2], Atul Jindal[3], Veer Bahadur Singh[4], Naveen Chander Reddy Podduturi[5], Shubhadeep Sinha[6], Sreenivasa Chary Sriramadasu[6]

*[1]VHS Infectious Diseases Medical Centre, Chennai, India, [2]Calcutta School of Tropical Medicine, Kolkata, India, [3]All India Institute of Medical Sciences, New Delhi, India, [4]Jawahar Lal Nehru Medical College, Ajmer, India, [5]AIG Hospitals, Hyderabad, India, [6]Hetero Labs Limited, Hyderabad, India*

**Background:** To improve the management of SARS-Co2 infection there is an urgent unmet need for an orally administered antiviral drug to prevent disease progression, hospitalization, and clinical complications. Molnupiravir was developed in response to this need. This study assesses its efficacy and safety in Indian patients with mild SARS-CoV2 infection.

**Methods:** This study is a phase III multi-centre open label randomized controlled trial of oral molnupiravir plus standard of care (MOL/SOC) versus SOC alone in Indian adults with mild SARS-CoV2 infection. The molnupiravir formulation used was developed and manufactured by HETERO LABS LTD, Hyderabad, India, under license from MERCK INC, NJ, USA. Eligible patients with RT PCR-confirmed mild SARS CoV2 infection, uncomplicated upper respiratory tract infection, with mild symptoms without any evidence of breathlessness, were randomized 1:1 to either oral MOL 800 mg b.i.d. for 5 days plus SOC or SOC alone. The primary endpoint was rate of hospitalization up to day 14. Secondary endpoints included proportion with a 2-point improvement in WHO 11-Point Clinical Progression Scale and rate of SARS CoV2 RT PCR negativity in naso/oropharyngeal swab at day 5, 10 and 14 and incidence of adverse events.

**Results:** Of 1284 patients screened, 1218 were eligible and randomized, 608 to MOL+SOC, and 610 to SOC. The population consisted mainly of male patients (68%). Both arms were well balanced for age, height and weight. In the MOL/SOC arm 9 patients (1.5%) required hospitalisation vs. 26 (4.3%) in the SOC arm ($p<0.01$). In the MOL/SOC arm 80.8%, 95.6% and 97.4% had clinical improvement by Day 5, 10 and 14, respectively, compared to 32.1%, 74.3% and 94.1% in the SOC arm ($p<0.0001$ at day 5 and 10, and $<0.01$ at day 14). The rate of SARS CoV2 negativity was 77.1%, 91.3% and 93.9% in MOL/SOC vs. 29.3%, 70.2% and 89.0% in SOC at day 5, 10 and 14, respectively ($p<0.001$). There were no serious adverse events. Mild and self-limiting adverse events occurred in 4.8% of MOL/SOC and 2.6% of SOC participants. The most common adverse events were neurological (headache, somnolence) and gastrointestinal.

**Conclusion:** A lower rate of hospitalisation, earlier clinical improvement, and earlier SARS CoV2 RT PCR negativity document superiority of Molnupiravir to SOC in mild SARS-CoV2 infection in this trial in India. Molnupiravir was well tolerated: adverse events were mild and rare.

## 102 INTRAMUSCULAR SOTROVIMAB IS NONINFERIOR TO INTRAVENOUS SOTROVIMAB FOR COVID-19

Late Breaking

**Adrienne E. Shapiro**[1], Elias Sarkis[2], Jude Acloque[3], Yaneicy Gonzalez-Rojas[4], Rubaba (Ruby) Hussain[5], Erick Juarez[6], Jaynier Moya[7], David Inman[8], Andrew Skingsley[9], Daren Austin[10], Amanda Peppercorn[11], Jennifer E. Sager[12], Elizabeth Alexander[12], Leah A. Gaffney[12], Anita Kohli[13]

*[1]Departments of Global Health and Medicine, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]Sarkis Clinical Trials, Gainesville, FL, USA, [3]BioClinical Research Alliance, Miami, FL, USA, [4]Optimus U Corporation, Miami, FL, USA, [5]Prime Global Research, Inc., Bronx, NY, USA, [6]Florida International Medical Research, Miami, FL, USA, [7]Pines Care Research Center, Pembroke Pines, FL, USA, [8]GlaxoSmithKline, Stevenage, UK, [9]GlaxoSmithKline, GSK House, Middlesex, UK, [10]GlaxoSmithKline, Brentford, UK, [11]GlaxoSmithKline, Cambridge, MA, USA, [12]Vir Biotechnology, Inc, San Francisco, CA, USA, [13]The Institute for Liver Health – Tuscon, Phoenix, AZ, USA*

**Background:** Sotrovimab is a pan-sarbecovirus neutralizing monoclonal antibody shown to be safe and effective for the treatment of early COVID-19 in high-risk patients and retains activity against variants of concern, including delta and omicron. To facilitate wider access to sotrovimab, it was formulated to allow for either intramuscular (IM) or intravenous (IV) administration.

**Methods:** COMET-TAIL (NCT04913675) is a Phase III, randomized, multicenter, open-label, noninferiority (NI) study of IM vs IV sotrovimab for the treatment of mild/moderate COVID-19 in participants ≥12 years of age at high risk of disease progression. Participants were randomized to receive sotrovimab by single 500 mg IV infusion or IM injection (500 mg or 250 mg). The primary objective was to evaluate the efficacy of 500 mg IM vs 500 mg IV sotrovimab in preventing hospitalization for >24 hours for acute management of illness due to any cause or death. The 250 mg IM arm discontinued early due to a greater number of hospitalizations seen in that arm. A 3.5% NI margin on the risk difference scale was prespecified.

**Results:** COMET-TAIL enrollment occurred from Jun-Aug 2021, coinciding with a surge in the SARS-CoV-2 delta variant in southern USA. The majority (~85%) of participants were Hispanic or Latino and ~25% were ≥65 years of age. In the 500 mg IM sotrovimab arm, 10/376 (2.7%) participants compared with 5/378 (1.3%) in the sotrovimab 500 mg IV arm met progression criteria for the primary endpoint (adjusted risk difference: 1.07% [95% CI: –1.25%, 3.39%]), meeting the NI margin of 3.5%. The overall rate of adverse events and injection/infusion-related reactions was low and similar between the 500 mg treatment arms. Most injection-site reactions were mild (grade 1), occurred shortly after dosing, and were limited in duration. Disease-related events (DREs) were balanced between the 500 mg IV and 500 mg IM arms. The most frequent DREs were COVID-19 pneumonia and pneumonia. There was a low percentage of participants (~1%) with serious adverse events across all treatment arms, and none were considered related to treatment. Two participants (1 with BMI 69 mg/kg2 and an 82-year-old man) in the 500 mg IM arm died due to progression of COVID-19; no deaths occurred in the 500 mg IV arm.

**Conclusion:** In the COMET-TAIL trial, sotrovimab given by 500 mg IM injection was found to be noninferior to IV infusion and was well tolerated. The option of IM administration will expand the potential for outpatient treatment with sotrovimab.

## 103 EFFECT OF SEROSTATUS ON THE EFFICACY OF SOTROVIMAB IN PREVENTING COVID-19 PROGRESSION

Late Breaking

**Anil Gupta**[1], Elias Sarkis[2], Andrea L. Cathcart[3], Elizabeth Alexander[3], Wendy W. Yeh[3], Megan Smithey[3], Nicola Scott[4], Andrew Skingsley[5], Helen Watson[5], Melissa Aldinger[3], Adrienne E. Shapiro[6]

*[1]Albion Finch Medical, William Osler Health Centre, Toronto, Canada, [2]Sarkis Clinical Trials, Gainesville, FL, USA, [3]Vir Biotechnology, Inc, San Francisco, CA, USA, [4]GlaxoSmithKline, Stevenage, UK, [5]GlaxoSmithKline, GSK House, Middlesex, UK, [6]Departments of Global Health and Medicine, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

**Background:** Sotrovimab is a pan-sarbecovirus monoclonal antibody clinically evaluated for prevention of progression of COVID-19 in high-risk patients early in the course of infection. We investigated the rate of prevention of hospitalization or death by baseline anti-SARS-CoV-2 serostatus.

**Methods:** COMET-ICE (NCT04545060) was a multicenter, double-blind, Phase III trial in nonhospitalized adults with symptomatic COVID-19 and ≥1 risk factor for disease progression. Participants were randomized 1:1 to an IV infusion of

sotrovimab 500 mg or placebo. The primary efficacy endpoint was all-cause hospitalization >24 hours or death due to any cause within 29 days. Anti-nucleocapsid SARS-CoV-2 antibody was measured by the Abbott SARS-CoV-2 IgG assay run on the Architect i2000SR immunoassay analyzer.

**Results:** In the final dataset (N=1057), the adjusted relative risk (RR) reduction in all-cause hospitalization or death due to any cause in the sotrovimab group compared to the placebo group was 79% (p<0.001) at Day 29. 70% and 19% of participants were seronegative and seropositive for anti-nucleocapsid protein at baseline, respectively. 11% of participants had unknown antibody status and were excluded. In the seronegative subgroup, 4/365 (1%) participants in the sotrovimab group met the primary endpoint compared to 26/375 (7%) in the placebo group (84% reduction in risk [RR: 0.16; 95% CI: 0.06, 0.45]). Of the 4 seronegative participants who received sotrovimab and met the primary endpoint, 1 participant was hospitalized for small intestinal obstruction that was likely unrelated to COVID-19. Two of the 26 seronegative participants in the placebo arm who met the primary endpoint died compared to no deaths in the sotrovimab group. In the seropositive subgroup, conclusions are limited by small numbers. Numerically fewer participants in the sotrovimab group (2/105, 2%) were hospitalized compared to the placebo group (4/97, 4%). Importantly, both hospitalized seropositive participants in the sotrovimab group had an alternative reason for their hospitalization that was likely unrelated to COVID-19 (diabetic foot ulcer, non-small cell lung cancer). Progression rates in the sotrovimab arm were low and similar regardless of serostatus (1% seronegative, 2% seropositive). Safety profile by serostatus was consistent with that reported in the overall population.

**Conclusion:** Sotrovimab appeared to consistently reduce the likelihood of a COVID-19-related hospitalization or death regardless of baseline serostatus.

## 104 CASIRIVIMAB AND IMDEVIMAB COMBINATION PROVIDES LONG-TERM PROTECTION AGAINST COVID-19

Late Breaking

**Meagan P. O'Brien**[1], Gary Herman[1], Eduardo Forleo Neto[1], Neena Sarkar[1], Flonza Isa[1], Peijie Hou[1], Kuo-Chan Chen[1], Ruanne Barnabas[2], Myron S. Cohen[3], John D. Davis[1], Kenneth C. Turner[1], Andrea T. Hooper[1], George D. Yancopoulos[1], David M. Weinreich[1]

*[1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, [2]University of Washington, Seattle, WA, USA, [3]Institute for Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** A previous report showed that a single 1200 mg subcutaneous (SC) dose of casirivimab and imdevimab (cas/imd) prevented symptomatic COVID-19 by 81.4% and reduced all SARS-CoV-2 infections (symptomatic and asymptomatic) by 66.4% in household contacts living with recently infected individuals over a 28-day period. While highly effective vaccines now exist for the prevention of COVID-19, a significant unmet need remains in patients who are unable to mount or maintain an adequate immune response to vaccination. Here we present additional results from 7-month follow-up period of the aforementioned study.

**Methods:** In this randomized, double-blind, placebo-controlled Phase III trial, asymptomatic participants exposed to a SARS-CoV-2–infected household member were randomized 1:1 to a single SC dose of placebo or 1200 mg cas/imd (600 mg of each monoclonal antibody). Efficacy analyses include participants who were RT-qPCR negative for SARS-CoV-2 (no current infection) and seronegative for SARS-CoV-2 (no prior infection) at baseline. The trial consisted of a primary efficacy assessment period of 28 days (Month 1) and a 7-month follow-up period (Months 2–8).

**Results:** Results from 842 placebo and 841 cas/imd RT-qPCR negative/seronegative enrolled participants (data through 04Oct2021, prior to emergence of Omicron) are presented. During the entirety of the 8-month study, cas/imd reduced the risk of symptomatic SARS-CoV-2 infections by 81.2% versus placebo (nominal P<0.0001; Table) and all SARS-CoV-2 infections (symptomatic and asymptomatic) by 68.2% versus placebo (nominal P<0.0001; Table). During Months 2–5, the risk of symptomatic and all infections were reduced by 100% and 89.5%, respectively (nominal P<0.0001). During Months 6–8 there was a resumption of symptomatic and all SARS-CoV-2 infections in the cas/imd group (19.9%; nominal P=0.6411 and 30.7%; nominal P=0.3967 risk reduction, respectively). Fewer cas/imd participants had a medically-attended visit versus placebo during the 8-months (1/841 [0.1%] vs 16/842 [1.9%], respectively). No new safety signals were identified for cas/imd during the follow-up period.

**Conclusion:** During the 8-month study period, a 1200 mg SC dose of cas/imd prevented SARS-CoV-2 infections, with maximal protection through Month 5. The prolonged protection supports the use of cas/imd for the long-term prevention of COVID-19 against susceptible variants, offering a pre-exposure prophylaxis strategy for individuals who are unlikely to respond or be protected by vaccination.

**Table. SARS-CoV-2 infection by study time period**

| Time period | Cas/imd 1200 mg SC (N=841) Total (%) | Placebo (N=842) Total (%) | Relative risk reduction % | Odds ratio (95% CI) | Nominal *P*-value |
|---|---|---|---|---|---|
| ***Symptomatic SARS-CoV-2 infection*** | | | | | |
| 28-day EAP (Month 1) | 13 (1.5) | 70 (8.3) | 81.4 | 0.17 (0.09, 0.31) | <0.0001 |
| Follow-up (Months 2–8) | 8 (1.0) | 42 (5.0) | 80.9 | 0.18 (0.09, 0.39) | <0.0001 |
| Entire study (Day 1–Month 8) | 21 (2.5) | 112 (13.3) | 81.2 | 0.17 (0.10, 0.27) | <0.0001 |
| ***All SARS-CoV-2 infection (symptomatic or asymptomatic)*** | | | | | |
| 28-day EAP (Month 1) | 42 (5.0) | 122 (14.5) | 65.5 | 0.31 (0.22, 0.45) | <0.0001 |
| Follow-up (Months 2–8) | 13 (1.5) | 51 (6.1) | 74.5 | 0.24 (0.13, 0.45) | <0.0001 |
| Entire study (Day 1–Month 8) | 55 (6.5) | 173 (20.5) | 68.2 | 0.27 (0.20, 0.37) | <0.0001 |

Cas/imd, casirivimab and imdevimab; CI, confidence interval; EAP, efficacy assessment period; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, subcutaneous.

## 105 CAMOSTAT IS NOT EFFECTIVE FOR MILD-MODERATE COVID-19 IN A PHASE 2 TRIAL OF ACTIV-2

Late Breaking

**Nikolaus Jilg**[1], Kara W. Chew[2], Mark Giganti[3], Eric S. Daar[4], David A. Wohl[5], Arzhang Cyrus Javan[6], Amy Kantor[3], Atasi Jana[7], Philip A. Hart[8], Joseph J. Eron[5], Judith S. Currier[2], Michael Hughes[3], Davey M. Smith[9], Jonathan Li[10]

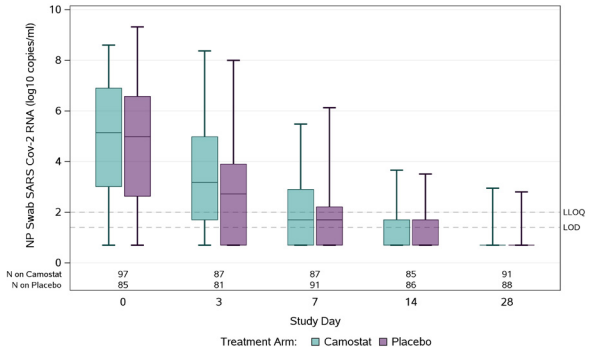
*[1]Massachusetts General Hospital, Boston, MA, USA, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]Harvard TH Chan School of Public Health, Boston, MA, USA, [4]Harbor–UCLA Medical Center, Torrance, CA, USA, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, [7]Sagent Pharmaceuticals, Schaumburg, IL, USA, [8]The Ohio State University, Columbus, OH, USA, [9]University of California San Diego, San Diego, CA, USA, [10]Brigham and Women's Hospital, Boston, MA, USA*

**Background:** Camostat, a serine protease inhibitor, prevents activation of the SARS-CoV-2 spike protein and blocks SARS-CoV-2 infection in vitro. We studied the safety and antiviral and clinical efficacy of orally administered camostat in non-hospitalized adults with mild-moderate COVID-19.

**Methods:** ACTIV-2/A5401 is a platform trial to evaluate therapies for non-hospitalized adults with mild-moderate COVID-19. In a Phase II portion of the study, participants were enrolled within 10 days of COVID-19 related symptom onset and randomized to camostat 200 mg orally every 6 hours for 7 days or the pooled placebo group. Objectives were to evaluate the safety and efficacy of camostat to reduce the duration of COVID-19 symptoms and increase the proportion of participants with SARS-CoV-2 RNA below the lower limit of quantification (LLoQ) from nasopharyngeal (NP) swabs on days 3, 7, and 14. Participants completed a study diary from day 0 to day 28 scoring COVID-19 symptoms as absent, mild, moderate, or severe.

**Results:** Of the 224 participants enrolled from 54 US sites, 215 participants (108 camostat, 107 placebo) initiated study intervention and formed the modified intent-to-treat population. Fifty-four percent were female, >99% cis-gender, 85% White, 9% Black, and 51% Latinx. Median age was 37 years; 47% reported ≤5 days of symptoms at study entry and 26% met the protocol definition of higher risk of progression to severe COVID-19. Most frequent symptoms on day 0 were cough (86%), fatigue (85%), nasal obstruction/congestion (71%) and body/muscle aches (71%). There was no significant difference between camostat and placebo arms in grade 3 or higher adverse events (7.4% vs. 6.5%, respectively). Median (Q1, Q3) time to symptom improvement was 9 days for both camostat (5, 20) and placebo (6, 19). There were no significant differences in the proportion of participants with NP SARS-CoV-2 RNA<="" div="">

**Conclusion:** Camostat was well-tolerated. Despite compelling in vitro data, camostat did not show evidence of antiviral or clinical efficacy in ACTIV-2/A5401. This highlights the critical importance of randomized controlled trials in the evaluation of therapies for COVID-19.




## 106 TREATMENT OF ANAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS TO PREVENT ANAL CANCER

Late Breaking

**Joel Palefsky**[1], Jeannette Lee[2], Teresa Darragh[1], Stephen Goldstone[3], Naomi Jay[1], Hillary Dunlevy[4], Timothy Wilkin[5], Isabella Rosa-Cunha[6], Abigail Arons[1], Julia Pugliese[7], Gary Bucher[8], Lisa Flowers[9], Rebecca Levine[10], Michael Berry-Lawhorn[1]

*[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [3]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [4]University of Colorado Denver, Denver, CO, USA, [5]Weill Cornell Medicine, New York, NY, USA, [6]University of Miami, Miami, FL, USA, [7]Emmes Corporation, Rockville, MD, USA, [8]Anal Dysplasia Clinic Midwest, Chicago, IL, USA, [9]Emory University, Atlanta, GA, USA, [10]Montefiore Medical Center, Bronx, NY, USA*

**Background:** The incidence of anal cancer is substantially higher among people living with HIV (PLWH) than the general population. Similar to cervical cancer, anal cancer is preceded by high-grade squamous intraepithelial lesions (HSIL). Treatment of cervical HSIL reduces cervical cancer incidence; however, there are no prospective studies of screening for and treatment of anal HSIL to prevent anal cancer.

**Methods:** Randomized controlled trial of anal HSIL treatment to reduce anal cancer incidence compared with active monitoring (AM). PLWH ≥35-years-old were screened for anal HSIL using high-resolution anoscopy (HRA). Eligible PLWH with biopsy-proven anal HSIL were randomized 1:1 to AM without treatment or HSIL treatment using modality-specific algorithms with repeated treatment for recurrent or persistent HSIL until HSIL was completely resolved. All participants underwent HRA at least every six months with biopsies for suspected ongoing HSIL in the treatment arm, annually in the AM arm, or any time in either arm if there was concern for cancer. The primary endpoint was time-to-incident anal cancer. Sample size estimates required 31 cancer cases for the primary analysis.

**Results:** 10,723 PLWH were screened at 25 US sites. 2,237 PLWH were randomized to the treatment arm and 2,222 to the AM arm. 4,446 (99.7%) were included in the time-to-incident cancer analysis. There were no differences between arms in gender identity, race/ethnicity, CD4 count or HIV viral load at randomization (Table). Most participants were treated with office-based electrocautery (92.7%). 8.2% had topical 5-fuorouracil cream or imiquimod. 9 anal cancer cases were diagnosed in the treatment arm and 21 in the AM arm. With a median follow-up of 25.8 months, the observed cancer incidence in the treatment arm was 173/100,000 PY of follow-up, compared with 402/100,000 PY in the AM arm, a 57% reduction in anal cancer (95%CI 6%-80%, P=.029 by log-rank test). There were 7 study-related serious adverse events (3 pain, 3 abscess, 1 ulceration) in the treatment arm and 1 soft tissue infection in the AM arm.

**Conclusion:** Treatment of HSIL, primarily with office-based electrocautery led to a significant reduction in anal cancer incidence. Treatment was well-tolerated. Anal cancer incidence was higher than expected in the AM arm. These data support inclusion of screening and treating anal HSIL as standard of care for anal cancer prevention in PLWH ≥35-years-old. Our data are also likely relevant for other groups at risk of anal cancer.

Demographics of the randomized study population

| | Randomized population | | P value[1] |
|---|---|---|---|
| | Treatment arm | Active monitoring arm | |
| | N=2,227 | N= 2,219 | |
| **Median age at randomization (years, interquartile range)** | 51.0 (44.0-57.0) | 51.0 (44.0-57.0) | 0.79 |
| **Gender identity N (%)** | | | 0.30[2] |
| Male | 1793 (80.5) | 1782 (80.3) | |
| Female | 346 (15.5) | 365 (16.5) | |
| Transgender | 85 (3.8) | 68 (3.1) | |
| Neither male nor female | 2 (0.1) | 2 (0.1) | |
| Decline to answer | 1 (0.0) | 2(0.1) | |
| **Race/ethnicity N (%)** | | | 0.37 |
| Non-Hispanic White | 695 (31.2) | 737 (33.2) | |
| African-American | 935 (42.0) | 939 (42.3) | |
| Hispanic, non-African-American | 381 (17.1) | 339 (15.3) | |
| Asian/Pacific Islander | 27 (1.2) | 29 (1.3) | |
| Other/Unknown | 189 (8.5) | 175 (7.9) | |
| **CDC HIV risk group N (%)[3]** | | | |
| Homosexual | 1738 (78.0) | 1742 (78.5) | 0.71 |
| Heterosexual | 532 (23.9) | 510 (23.0) | 0.48 |
| Injection drug use | 152 (6.8) | 177 (8.0) | 0.14 |
| Transfusion | 53 (2.4) | 47 (2.1) | 0.56 |
| Hemophilia | 2 (0.1) | 4 (0.2) | 0.41 |
| Other high-risk group | 34 (1.5) | 27 (1.2) | 0.37 |
| **Plasma HIV-1 RNA copies/mL at randomization N (%)[4]** | | | 0.27 |
| <50 | 1852 (83.7) | 1800 (81.8) | |
| 51-199 | 155 (7.0) | 160 (7.3) | |
| 200-1000 | 83 (3.8) | 93 (4.2) | |
| >1000 | 122 (5.5) | 148 (6.7) | |
| **CD4 cells/uL at randomization (median, interquartile range)[5]** | 602 (393-827) | 607 (410-837) | 0.32 |

[1]The Wilcoxon rank sum test was used to compare arms with respect to continuous variables (age, years from HIV diagnosis and CD4 count). Pearson's chi-square test was used to compare arms with respect to categorical variables.
[2]Based on comparing the two groups with respect to 3 categories of gender identify (male, female and transgender)
[3]Numbers exceed 100% because some participants classified themselves in more than one category
[4]Data missing on 15 treatment arm and 18 monitoring arm participants
[5]Data missing on 6 treatment arm and 12 monitoring arm participants

## 107 THE HIV-1 PROVIRAL LANDSCAPE: WHAT HAVE WE LEARNED?

**Sarah Palmer**[1]

*[1]The Westmead Institute for Medical Research, Westmead, Australia*

Genetic characterization of HIV-1 proviruses isolated from CD4+ T cells of individuals on effective antiretroviral therapy has revealed that only 2-12% of persistent HIV-1 is genetically-intact and potentially replication-competent. Replication-competent proviruses are the main barrier to HIV-1 eradication as they contribute to viral rebound if therapy is interrupted. Therefore, determining the source of latent replication-competent HIV-1 is important for identifying targets for future eradication strategies. Resting memory CD4+ T cells are a well-defined reservoir of latent HIV-1, however, several research groups have shown that this replication-competent HIV-1 is disproportionally distributed within different CD4+ T cell subsets. The different subsets of memory CD4+ T cells exhibit unique qualities that likely affect the genetic landscape of persistent HIV-1. In this presentation, we will explore the HIV-1 proviral landscape within CD4+ T cells subsets and identify potential cellular and viral mechanisms which contribute to the persistence of genetically-intact and defective HIV-1 proviruses within these subsets during therapy. Identifying and targeting these mechanisms will be critical for developing future curative strategies.

## 108 ROLE OF SELECTION PRESSURES AND IMMUNE RESPONSES IN SHAPING THE PERSISTENT RESERVIOR

**Francesco R. Simonetti**[1]

*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Antiretroviral therapy alone cannot eradicate HIV-1 infection due to the persistence of viral genomes stably integrated into latently infected CD4+ T cells. It is now clear that the HIV-1 reservoir is not a static collection of long-lived cells infected before therapy, but rather a highly dynamic population of clones of variable sizes. Here we will describe some of the many factors affecting the survival (or the loss) of HIV-1-infected cells shaping reservoir composition over time. Given the striking heterogeneity of T cells and the proviruses they harbor, no single factor can explain the persistence of all infected cells. We will explore these features based on whether they belong to i) the provirus, ii) its genomic location, or iii) T cell biology. We will discuss how intact and defective proviruses differentially decay on ART and may be under distinct selective pressure when expressed. However, given that only a fraction of cells within a clone expresses HIV-1 at any given time, and at levels too low to produce virions, most cells persist regardless of the proviral structure. We will then focus

on the role of HIV-1 integration. Proviruses causing the misexpression of host genes can result in either detriment or survival advantage for infected cells. However, integrations in only a handful of genes showed significant enrichment of proviruses (mostly defective) in individuals on ART. Recent data suggest that intact proviruses in heterochromatic regions, such as centromeres and specific Zinc finger (ZNF) gene clusters, are positively selected due to deeper latency. Stimuli driving the survival and proliferation of infected cells can favor the maintenance of certain clones. Homeostatic signals can lead to cell division without latency reversal, but they unlikely result in the clonal sizes observed in vivo. Here we propose that physiological TCR engagement only rarely elicits HIV expression. Indeed, adaptive immune responses to chronic antigens, especially those characterized by memory inflation, can result in large clones regardless of the site of HIV-1 integration. However, certain proviruses may be selected thanks to the synergy between recurrent antigenic stimulation and proviral insertional effects. Finally, we will discuss immune selective pressures on viruses leading to rebound upon treatment interruption, including antigen specificity of the cell, and the provirus sensitivity to interferon, CTLs, and autologous antibodies.

### 109 NOVEL IMMUNOTHERAPY-BASED CURE INTERVENTIONS

**Mirko Paiardini**[1]
[1]*Emory University, Atlanta, GA, USA*

The development of single-pill anti-retroviral therapies (ART) with tolerable toxicity profiles have proven highly effective in suppressing HIV viremia to clinically undetectable levels in people living with HIV (PLWH). However, ART alone is incapable of purging the pool of long-lived, tissue-resident, quiescent CD4+ T-cells harboring latent, replication-competent viral genomes. These "viral reservoirs", maintained despite ART, comprise cells enriched for the expression of co-inhibitory receptors (Co-IR), which enforce state of T cell exhaustion. In this presentation, I will discuss advances in using strategies targeting T cell exhaustion and homeostasis to induce viral reactivation during ART and viral control in absence of ART in SIV-infected rhesus macaques (RMs). In addition to PD-1+ T follicular helper cells (TFH), lymph node CTLA-4+ CD4+ T cells harbor robust levels of replication competent SIV-DNA. To stimulate the activation of Co-IR-expressing T cells, we have performed combination blockades of PD-1 and CTLA-4 during ART, which synergized to induce T cell proliferation and resulted in clonally diverse plasma viral reactivation. As the blockade failed to enhance the activity of SIV-specific T-cell responses, these data suggest that the reversal of T-cell exhaustion alone, in the absence of viral antigen, is insufficient to stimulate a reduction of viral content in tissue. Furthermore, concurrent studies utilizing CD8 depleting mAbs described a role for CD8+ T cells in regulating viral latency via non-cytolytic mechanisms. Notably, our most recent data shows that interleukin(IL)-10 signaling, which regulates T cell survival, differentiation and Co-IR expression, promotes viral persistence. Consistently, in an ongoing nonhuman primate study simultaneous IL-10 neutralization and PD-1 blockade performed following ART analytical therapy interruption synergized to induce viral control. In summary, our data demonstrates that strategies targeting the maintenance of the cells known to harbor the viral reservoir in combination with improving antiviral responses might represent a novel approach to control viremia in the absence of ART. Understanding how these complex processes promote viral persistence and how they might be further targeted by emerging therapeutics represent both a formidable challenge and an exciting opportunity for the years to come.

### 110 TREATMENT SHORTENING FOR DRUG-SUSCEPTIBLE TB: WHERE ARE WE AND WHAT'S NEXT?

**Susan Dorman**[1]
[1]*Medical University of South Carolina, Charleston, SC, USA*

Identification of short, well-tolerated treatments for drug-susceptible pulmonary TB has been a priority since the advent of combination antimicrobial treatment approximately 70 years ago. Considerable progress – including recent progress – has been made, but more is needed. The goal of this session is to provide a contemporary overview of the state of the field, including what is on the horizon, with regard to shortening the duration and increasing the tolerability of treatments for drug-susceptible TB. This session will describe recent clinical trial data on antimicrobial regimens to shorten TB treatment in adults and children, including those living with HIV. A role for individualized therapy that takes into account pre-treatment and on-treatment patient factors will be discussed, and the potential for novel biomarkers and novel trial designs to augment trial efficiency will be explored. Perspectives on how we might take critical next steps will be examined.

### 111 A NEW ERA FOR TREATMENT OF MULTI-DRUG RESISTANT TUBERCULOSIS

**David Moore**[1]
[1]*London School of Hygiene & Tropical Medicine, London, UK*

After decades of treating drug-resistant tuberculosis with 18-24 month regimens of highly unpleasant multi-drug regimens consisting of 5-8 agents including an ototoxic daily injectable drug, achieving treatment success in less than half of all patients, we are entering a new therapeutic era. New and repurposed agents are important but the laboratory and clinical science underpinning their deployment has also been critical in the rapid transformation of the multidrug-resistant TB (MDR-TB) therapeutic landscape. Moving from highly toxic and ineffective MDR-TB treatment regimens based upon well-meaning but inexpert 'expert opinion' to evidence-based effective, well-tolerated short-course, all oral regimens is testimony to the value of rigorous scientific endeavour. The evolution of the approach to treatment of MDR-TB treatment over the past decade will be described, from the 'Bangladesh regimen' through to the BPaL/BPaL+ approach evaluated in NIX-TB and TB-PRACTECAL. Looking to the future the presentation will end by highlighting work in progress for which reporting is eagerly awaited, including the potentially paradigm-shifting TRUNCATE-TB trial and three trials of preventive therapy for contacts exposed to MDR-TB.

### 112 THE PROMISE OF NEW DRUGS AND LONG-ACTING INJECTABLES FOR TB TREATMENT AND PREVENTION

**Eric Nuermberger**[1]
[1]*The Johns Hopkins University, Baltimore, MD, USA*

New drugs in clinical trials and long-acting injectable formulations have the potential to meet critical unmet needs in the treatment and prevention of tuberculosis, including shorter regimens, improved safety, and expanded options for drug-resistant tuberculosis. This presentation will provide an update on new drugs in early clinical development and describe how long-acting injectable formulations could address important obstacles to ending the world's oldest pandemic.

### 113 THE STATE OF STI EPIDEMICS AND RESPONSE IN THE UNITED STATES

**Mena L. A.**[1]
[1]*Centers for Disease Control and Prevention, Atlanta, GA, USA*

STIs in the United States are at an all-time high with reported cases of chlamydia, gonorrhea, and syphilis increasing for the sixth consecutive year in 2019. Yet not long ago, gonorrhea rates were at historic lows, and syphilis was close to elimination. Now congenital syphilis is rising dramatically, and the threat of antibiotic resistant gonorrhea grows. Addressing the rise in STIs will require coordinated efforts, research, and innovation to use resources efficiently and to promote holistic, equitable approaches. These infections remain common, are costly, and challenge the health and wellness of millions of people. This session will discuss current epidemiology and trends in STI incidence and morbidity and the challenges and opportunities that exist in curbing STIs.

### 114 CURRENT AND FUTURE RESEARCH IN STI VACCINES

**Sinead Delany-Moretlwe**[1]
[1]*Africa Centre for Population Health, Mtubatuba, South Africa*

More than one million sexually transmitted infections (STIs) are acquired every day worldwide. Untreated STIs have a significant impact on the sexual and reproductive health of populations and can lead to pregnancy complications, infertility, and cancers as well as increase HIV transmission. STIs and their complications are associated with stigma and considerable social and economic consequences. Rising antimicrobial resistance, especially for gonorrhea, is seen as a major threat to global public health. The development of vaccines against a range of STI pathogens is therefore a critical public health goal. In this presentation the lessons learned from the successful development and introduction of the HPV vaccine will be reviewed. Updates on the latest evidence for simplified dosing regimens will be presented, as well as current research gaps. The vaccine development pipeline for other STIs including HSV, gonorrhea, chlamydia, syphilis, and trichomonas will be reviewed, and progress and development challenges summarized. Finally, considerations for implementation of these future vaccines will be discussed, with a focus on current evidence needs to inform future delivery strategies in a range of settings and populations, particularly in the context of rising vaccine hesitancy.

**115 SEXUALLY TRANSMITTED INFECTIONS PROPHYLAXIS, IS THIS THE ANSWER?**

**Elizabeth A. Bukusi**[1]
[1]*Kenya Medical Research Institute, Kilifi, Kenya*

This talk will discuss the options of STI prevention in the context of pre-exposure prophylaxis (PrEP) for HIV prevention. With the expansion of both HIV PrEP and anti-viral treatment for HIV over the last decade there has co incidentally been a global surge in incident STI infections notably with the most evaluated being infections caused by Neisseria Gonorrhea (GC), Chlamydia Trachomatis (CT) and Treponema Pallidum (Syphilis). Over 1 million curable STI's are diagnosed daily globally. This has been both among both the general population, and more marked among key populations. The knowledge of undetectable equals untransmittable (U=U and there has not been directly linked to this observation. Notably, there has also not been a reduction in the reporting of condomless sex. HIV PrEP has had a remarkably expansion especially in SSA, but there are challenges of high initiation, but adherence and persistence being inconsistent. STI antimicrobial prophylaxis has been explored in several studies and concerns are still raised around possible resistance to current antimicrobial agents as has been noted particularly with GC. The presentation will explore the options of prophylaxis of STI's management s and also suggest mechanisms for programmatic and research implications by drawing on research done globally with a focus on doxycycline for STI prophylaxis.

**116 NEW ANTIRETROVIRALS AND THE FUTURE OF HIV TREATMENT AND PREVENTION**

**Chloe L. Orkin**[1]
[1]*Queen Mary University of London, London, UK*

Where are we now and what will the future of HIV treatment and prevention hold? This plenary will describe current state-of-the-art therapy and prevention and consider what the perfect drug would look like. The current ARV pipeline will be evaluated with a focus on the following questions: Which classes and compounds are in development? How are they being partnered? How far along are the trials for both treatment and PrEP? Which endpoints have been reached and what do we know about safety and efficacy so far? Have any regulatory concerns arisen and how have they been dealt with? Which modalities are being paired with the various compounds? Could these modalities and compounds provide choices for all? What have we learned from the implementation of long-acting Cabotegravir and Rilpivirine so far and how can these lessons be applied to future modalities? What do we need to do to ensure that our study designs include under-represented groups in trials and protect women through rather than from research? How can we influence equity of access and secure the future therapies that would benefit patients globally? Are there individual actions that we could take to influence and create the future we want to see?

**117 PAST AND FUTURE OF HIV VACCINES**

**Mark Feinberg**[1]
[1]*International AIDS Vaccine Initiative, New York, NY, USA*

Now over 40 years since the initial reports of AIDS, and despite tremendous strides in the development of, and broader global availability to, highly efficacious antiretroviral therapy, global rates of new HIV infections continue at an unacceptably high level. While progress is also being made in developing novel biomedical HIV prevention interventions, an efficacious HIV vaccine will almost certainly be needed to end the AIDS pandemic. However, inherent properties of HIV-including its extraordinarily high levels of genetic diversity, the structural attributes of the viral surface Envelope glycoprotein, the ability of the virus to establish life-long infections, and its capacity to evade, avoid and damage host immune responses-make it the most challenging pathogen to ever confront vaccine developers. Traditional empiric vaccine approaches that have enabled the successful development of vaccines against a wide range of other infectious disease threats have so far failed to deliver an efficacious HIV vaccine. As a result, HIV vaccine research efforts have necessarily required the development of new tools and technologies for vaccine immunogen design, characterization, and evaluation. Without question, the scientific power and sophistication of HIV vaccine approaches have provided tremendous benefits for the accelerated development of vaccines against other global threats, including SARS-CoV-2. Contrasting the pace of HIV versus SARS-CoV-2 vaccine development programs vividly demonstrates how the biological nature of the pathogen being targeted, and how it interacts with the human immune system, as the fundamental determinants of timelines and probability of vaccine development success. Encouragingly, the innovative approaches for rational vaccine design pioneered in the pursuit of HIV vaccine development, in concert with elements emerging from accelerated COVID-19 vaccine development programs, are bringing new hope to efforts to develop an efficacious HIV vaccine itself. In particular, novel strategies for the design and expedited evaluation of HIV vaccine immunogens targeting the elicitation of broadly neutralizing antibodies are providing new directions and promise to the HIV vaccine field. This presentation will review the challenges, disappointments and lessons learned from earlier HIV vaccine development efforts, while also describing innovative strategies now being pursued and encouraging recent progress being made towards an efficacious HIV vaccine.

**118 INFLAMMASOMES AND IL-1B: AN INNATE IMMUNE AXIS IN CD4+ T CELLS DRIVING HIV INFECTION**

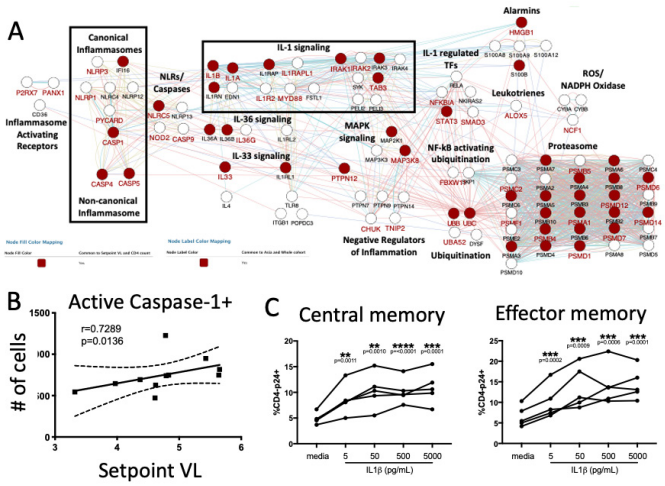
**Jeffrey A. Tomalka**[1], Khader Ghneim[1], Margaret Costanzo[2], Susan Pereira Ribeiro[1], Nelson L. Michael[3], Merlin Robb[2], Michael Eller[4], Rafick-Pierre Sékaly[1]
[1]*Emory University, Atlanta, GA, USA,* [2]*Henry M Jackson Foundation, Bethesda, MD, USA,* [3]*Walter Reed Army Institute of Research, Silver Spring, MD, USA,* [4]*National Institutes of Health, Bethesda, MD, USA*

**Background:** Early innate immune activation has a profound impact on modulating the generation of anti-HIV immune response. These responses vary between individuals based yet little is known about how this variance impacts disease outcome. Defining how pre-infection immune status impacts on immune responses post-HIV infection is critical for understanding HIV pathogenesis. In this study, we test our hypothesis that heightened IL-1β and inflammasome signaling pre-infection augments viral loads and dysregulated immune responses.

**Methods:** The RV217 acute infection cohort recruits high risk participants prior to confirmed HIV infection, with PBMCs banked bi-weekly prior to acquisition. We performed total RNA sequencing on PBMCs, innate cells and CD4+ T cells from the last visit prior to confirmed HIV and used gene expression analysis including GSEA to identify pre-infection IL-1β and inflammasome pathways as correlates of viral loads (VL) and CD4 counts post-infection. We probed pre-infection PBMCs for expression of NLRs, IL-1β and active caspase-1 using flow cytometry. We stimulated purified memory CD4+ T cells from healthy donors with IL-1β for 18 hours, infected the cells with HIV and quantified infection after 72 hrs by intracellular p24 staining.

**Results:** We found that heightened transcriptional activation of IL-1 and inflammasome pathways pre-infection was associated with higher VLs and lower CD4 counts, a finding consistent across males and females. A network of IL-1 and inflammasome genes associated to poor outcome is shown in Fig. 1A and demonstrates global priming across all levels of IL-1/inflammasome signaling. Using flow cytometry, we confirmed the critical role for this pre-infection signature by showing two clusters of cells, one with active caspase-1 and one with high IL-1β, were the only significant correlates of increased VLs and decreased CD4 counts (Fig. 1B). We validated a mechanistic role by showing that IL-1b pre-treatment significantly enhances HIV infection of memory CD4+ T cells (Fig. 1C).

**Conclusion:** The findings of our study provide new insight into how pre-existing inflammation can have a significant negative impact on HIV disease progression by promoting viral infection and decreasing CD4+ T cell counts. We further show that the effect of IL-1β can be direct on CD4+ T cells where it leads to higher levels of infection. These data highlight a specific form of inflammation that can be targeted therapeutically to reduce viral infection/spread and maintain CD4+ T cell levels.




## 119 RAPID LOSS OF CD4+ T CELLS BY PYROPTOSIS IN ACUTELY SIV-INFECTED RHESUS MACAQUES

New Investigator Scholar

**Xuan He**[1], Malika M. Boudries[1], John D. Ventura[1], Erica N. Borducchi[1], Abishek Chandrashekar[1], Michelle Lifton[1], Jinyan Liu[1], Dan Barouch[1]
*[1]Beth Israel Deaconess Medical Center, Boston, MA, USA*

**Background:** The mechanisms underlying depletion of CD4 T cells from multiple anatomic sites during acute HIV-1 infection are not well understood. Here we did comparative studies on cell death mechanisms in CD4 T cells from gut-associated lymphatic tissue (GALT), spleen and pelvic lymph nodes from rhesus macaques with pathogenic SIV infection.
**Methods:** 19 animals were infected with SIVmac251 by the intravaginal route, and were necropsied on day 0, 3, 7 and 10 following infection. At necropsy, multiple tissues including colon, spleen, mesenteric lymph nodes and pelvic lymph nodes were obtained. 7 monkeys were infected with SIVmac251 by intrarectal route, and blood were collected at multiple time points from day 0 to day 245.
**Results:** Peripheral blood CD4 T cells showed a modest increase of activated caspase 1 during acute SIV infection, which peaked on day 14 to the mean level of 5.5% following infection. In contrast, there was a dramatic increase of CD4 T cell pyroptosis observed on day 10 following challenge in multiple tissues, including average of 25.1% in colon, 10.6% in mesenteric lymph nodes (LN), 34.6% in spleen, and 17.6% in pelvic LNs. CD4 T cell pyroptosis showed strong negative correlation with the percentage of CD4 T cells from blood, GALT and lymphoid tissues in rhesus monkeys during early SIV infection. The upregulation of interferon-gamma inducible factor 16 (IFI16), a host DNA sensor that triggers pyroptosis, was also observed in tissue-resident CD4 T cells, and was associated with viral loads. In contrast, caspase-3-mediated apoptosis and viral cytotoxicity only accounted for a very small fraction of CD4 T cell death (< 5%), and alternative programmed cell death mechanisms, including mitochondria-induced caspase-independent cell death, necroptosis, and autophagy, did not significantly contribute to CD4 T cell depletion.
**Conclusion:** These data provide a strong in vivo evidence for a model in which caspase-1-mediated pyroptosis results in substantial CD4 T cell death in the GALT and lymphoid organs, and release of proinflammatory cytokines. These findings have important implications for our understanding of HIV-1 pathogenesis and for the development of therapeutic strategies to prevent HIV-1 immunopathogenesis.

## 120 EXPERIMENTAL MICROBIAL DYSBIOSIS ENHANCES RECTAL SIV ACQUISITION IN RHESUS MACAQUES

**Alexandra Ortiz**[1], Phillip Baker[1], Charlotte Langner[1], Jennifer Simpson[1], Jacob Flynn[1], Carly E. Starke[1], Carol Vinton[1], Brandon Keele[2], Jason Brenchley[1]
*[1]National Institutes of Health, Bethesda, MD, USA, [2]National Cancer Institute, Frederick, MD, USA*

**Background:** Alterations to the composition of the vaginal and rectal bacterial microbiomes are associated with localized inflammation and correlate with acquisition of some sexually transmitted pathogens such as HIV. Thus far, there have been no empirical assessments regarding the contribution of the intestinal microbiome to rectal lentiviral infection.
**Methods:** To directly assess the contribution of bacterial dysbiosis to rectal lentiviral acquisition, we induced dysbiosis in rhesus macaques prior to repeated, lose-dose intra-rectal challenge with SIVmac239X, utilizing the antibiotic vancomycin. Intestinal lymphocyte phenotype and function were assessed by flow cytometry, bacterial frequencies by 16S Illumina sequencing, and relative transcript quantification by Nanostring and qRT-PCR.
**Results:** Although no difference was noted in the number of challenges required for SIV acquisition, vancomycin administration led to significantly increased numbers of transmitted-founder variants detected upon SIV acquisition. Vancomycin-treated animals displayed decreased intestinal T-cell activation during acute SIV infection; however, these features did not distinguish between animals that acquired SIV at early versus late challenge. Early acquisition - irrespective of experimental dysbiosis - was associated with significantly reduced frequencies of rectal Th22 cells, with vancomycin-treated animals displaying a trend towards reduced Th22 frequencies. Th22 frequency correlated with the number of challenges required for infection. Significant differences in Ruminococcaceae, Gammaproteobacteria, and Prevotellaceae genera distinguished between early and late acquisition and were additionally perturbed in vancomycin-treated animals. Metagenomic inference further reveled that the microbiome of early-acquiring macaques was enriched for taxa containing pyrimidine metabolism genes. We confirmed that transcripts for the ROS-inducing receptor DUOX2 – which is overly responsive to pathobiont pyrimidine biosynthesis in cases of IL-22 insufficiency – were significantly upregulated in early-acquiring animals.
**Conclusion:** These findings experimentally demonstrate that intestinal dysbiosis contributes to gastrointestinal tract immunity and lentiviral acquisition across the epithelial barrier.

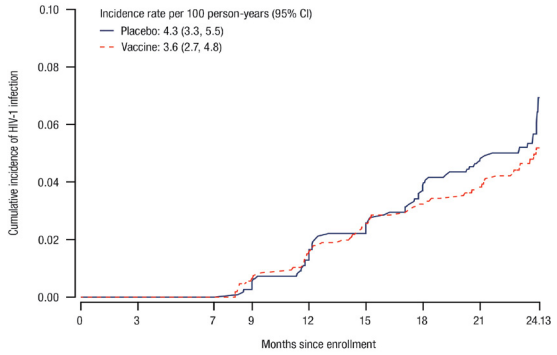
## 121 PHASE IIB EFFICACY TRIAL OF MOSAIC HIV-1 VACCINE REGIMEN IN AFRICAN WOMEN: IMBOKODO

**Glenda E. Gray**[1], Kathy Mngadi[2], Ludo Lavreys[3], Alex Luedtke[4], Steven Nijs[5], Daniel Stieh[6], Michal Juraska[7], Ollivier Hyrien[7], Edith Swann[8], Georgia Tomaras[9], Julie McElrath[7], Maria G. Pau[6], Susan P. Buchbinder[10], Frank Tomaka[11]
*[1]South Africa Medical Research Council, Cape Town, South Africa, [2]The Aurum Institute, Johannesburg, South Africa, [3]Janssen, Beerse, Belgium, [4]University of Washington, Seattle, WA, USA, [5]Janssen Infectious Diseases–Diagnostics BVBA, Beerse, Belgium, [6]Janssen Vaccines & Prevention BV, Leiden, Netherlands, [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [8]National Institute of Allergy and Infectious Disease, Bethesda, MD, USA, [9]Duke University, Durham, NC, USA, [10]San Francisco Department of Public Health, San Francisco, CA, USA, [11]Janssen Research & Development, Titusville, NJ, USA*

**Background:** Imbokodo is the first trial evaluating clinical efficacy of a heterologous HIV-1 vaccine regimen consisting of an Ad26 vector (Ad26.Mos4.HIV) expressing mosaic Gag/Pol/Env antigens for broad HIV-1 clade coverage, and an aluminum-adjuvanted clade C gp140. This trial, conducted in women at high risk for HIV-1 in sub-Saharan Africa, is supported by preclinical and early phase clinical trials demonstrating safety and immunogenicity.
**Methods:** We enrolled 18-35 year-old women in a randomized, double-blind, placebo-controlled, Phase IIb efficacy trial in Malawi, Mozambique, South Africa, Zambia, and Zimbabwe. Women were randomized 1:1 to a heterologous prime and boost vaccine regimen or placebo administered at Months 0 and 3 (Ad26.Mos4.HIV) and Months 6 and 12 (Ad26.Mos4.HIV+clade C gp140). Pre-exposure prophylaxis was available at no charge. Primary vaccine efficacy (VE) was evaluated from Month 7 to 24 (VE[7-24]) in the per-protocol (PP) cohort. Continuation of the trial was to occur if the lower bound of the 95% confidence interval (CI) for VE(7-24) was >0%. Adverse events (AEs) were collected post each vaccination. Serious AEs and AEs of special interest (AESIs) were collected throughout the trial.
**Results:** A total of 2637 women (1323 placebo, 1314 vaccine), with a median age of 23 years, were enrolled at 23 sites. Baseline characteristics were similar across arms with ~3% detectable intracellular tenofovir disoproxil fumarate levels. HIV-1 incidence between Month 7 and 24 in the PP cohort was 4.3 per 100 person-years in the placebo arm versus 3.6 in the vaccine arm (Figure). VE(7-24) was 25.2% (95% CI: –10.5% to 49.4%). The vaccine was well tolerated with mild local reactogenicity (mild/moderate pain/tenderness: 23% placebo, 50% vaccine). Mild/moderate systemic symptoms were reported by 56% and 66% in the placebo and vaccine arms, respectively. No vaccine-related serious AEs or AESIs were reported.

**Conclusion:** HIV-1 incidence was high in this trial. Unfortunately, this vaccine regimen, although safe, did not provide statistically significant protection against HIV-1 infection in young women and, therefore, the trial was discontinued. An ongoing Phase III trial (Mosaico) is evaluating the efficacy of an HIV-1 vaccine regimen with a modified boost (Ad26/bivalent gp140) in MSM and transgender individuals in the Americas and Europe. Biomedical interventions are urgently required to reduce the impact of HIV-1 in women in Africa.

**Figure. Cumulative incidence of HIV-1 infection over time (per-protocol cohort*).**




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 1109 | 1109 | 1100 | 1092 | 1068 | 1049 | 1031 | 1007 | 161 |
| Vaccine | 1079 | 1079 | 1065 | 1054 | 1036 | 1014 | 993 | 977 | 156 |
| **Cumulative HIV-1 infections** | | | | | | | | | |
| Placebo | 0 | 0 | 0 | 3 | 18 | 28 | 42 | 51 | 63 |
| Vaccine | 0 | 0 | 0 | 6 | 17 | 27 | 34 | 40 | 51 |

*The per-protocol cohort was defined as women who were HIV-1 uninfected 4 weeks after the third vaccination visit, received all planned vaccinations at the first 3 vaccination visits within the visit window, and did not have any other major protocol deviations judged to possibly impact the efficacy of the vaccine.

## 122 ADMINISTRATION OF 3BNC117 AT ART INITIATION INDUCES LONG-TERM HIV CD8 T-CELL IMMUNITY

New Investigator Scholar

**Míriam Rosás-Umbert**[1], Jesper D. Gunst[1], Rikke Olesen[1], Marina Caskey[2], Michel Nussenzweig[2], Martin Tolstrup[1], Ole Søgaard[1]
*[1]Aarhus University Hospital, Aarhus, Denmark, [2]The Rockefeller University, New York, NY, USA*

**Background:** In addition to their direct antiviral effect, broadly neutralizing antibodies (bNAbs) against HIV-1 may have a vaccinal effect by stimulating T cell-specific immunity via immune complex formation leading to dendritic cell activation and enhanced antigen processing and presentation. This effect has been shown to increase the chance of post-treatment control in SHIV-infected non-human primates. To determine whether a vaccinal effect also occurs in humans, we measured HIV-1-specific T cell immune responses in newly diagnosed HIV-1-infected individuals starting antiretroviral therapy (ART) with or without the potent bNAb 3BNC117.
**Methods:** Cryopreserved PBMCs were obtained from the eCLEAR study (NCT03041012) in which HIV-1-infected individuals starting ART were randomized to receive: 1) ART alone, 2) ART+3BNC117 at day 7 and 21 after ART initiation, 3) ART+romidepsin (RMD) at day 10, 17 and 24 after ART initiation or 4) ART+3BNC117+RMD. We used the activation-induced marker (AIM) assay to quantify HIV-1-specific T cell immune responses pre-ART, at 3 months and 12 months after ART initiation. HIV-1-specific CD4+ or CD8+ T cells were defined as PD-L1+4-1BB+, PD-L1+CD69+, CD69+4-1BB+ or PD-L1+4-1BB+CD69+ following peptide pool stimulations against either HIV-1 Env, Gag, Nef or Pol.
**Results:** At ART initiation, all 4 groups had comparable levels of HIV-1-specific CD4+ and CD8+ T cells responses towards HIV-1 Env, Gag, Nef and Pol; as expected, the pool of HIV-1-specific cells within the total CD8+ compartment contracted following ART initiation to 12 months into ART (median frequency of 2.67% vs 0.79%, p=0.01) while the CD4+ compartment were more sustained over time (median frequency of 1.86% vs 1.30%, p=0.33). However, the frequency of Gag-specific CD8+ T cells was significantly higher in individuals that received 3BNC117 (with or without RMD) at 3 months after starting ART compared to ART control group (median 0.69% vs 0.29%, respectively, p=0.04) and at 12 months of ART (median 0.91% vs 0.31% respectively, p=0.03).
**Conclusion:** Our results suggest that bNAb therapy at the time of ART initiation may have a vaccinal effect by inducing long-lasting Gag-specific T CD8+ cells responses, which have been associated with immune mediated virus control.

## 123 CD8+ LYMPHOCYTES MODULATE STEMNESS AND SURVIVAL PATHWAYS IN HIV-INFECTED CD4+ T CELLS

**Lavinia Franchitti**[1], Ashish A. Sharma[1], Jack Yoon[1], Erick R. White[1], Hong Wang[1], Maura Statzu[1], Abigail Willemse[1], Rafick-Pierre Sékaly[1], Mirko Paiardini[1], Guido Silvestri[1], Deanna Kulpa[1]
*[1]Emory University, Atlanta, GA, USA*

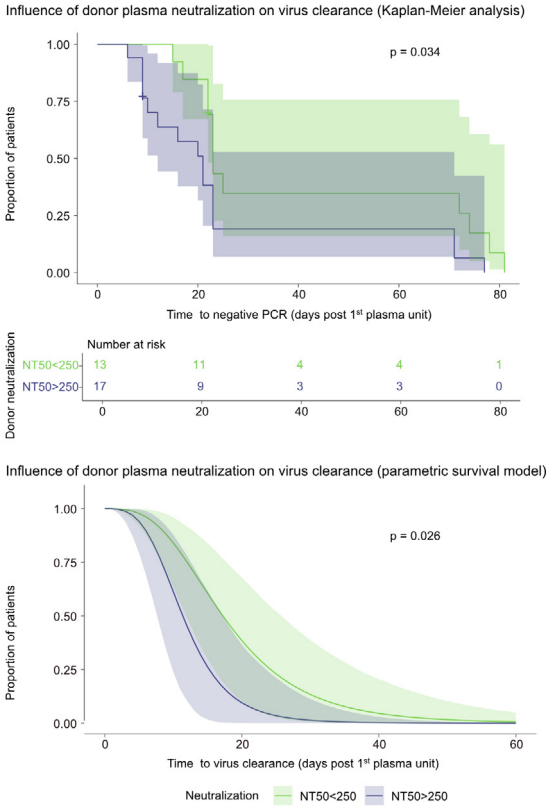
**Background:** The persistence of HIV infection under ART is due to a reservoir of latently infected cells that harbor replication-competent virus and evade immune recognition. Defining the mechanisms responsible for the establishment and maintenance of HIV latency is crucial to achieve HIV eradication or functional cure. Previous studies demonstrated that CD8+ T-cells inhibit virus replication during untreated HIV/SIV infection and inhibit virus production under ART; however, the mechanisms responsible for this antiviral effect remain poorly understood.
**Methods:** We used a primary cell-based in vitro latency model to examine non-cytotoxic suppression of HIV transcription by CD8+ T cells. Memory CD4+ T-cells from HIV-naïve individuals were infected in vitro and then co-cultured with activated autologous CD8+ T-cells in the presence of ART. To evaluate CD8+ T-cell suppression activity, we quantified HIV-gag expression by flow cytometry and integrated HIV DNA frequency by qPCR. We then employed a combination of high-dimensional and transcriptomic analyses to identify CD4+ T-cell signaling pathways differentially modulated by the co-culture with CD8+ T-cells.
**Results:** HIV expression in memory CD4+ T-cells was reduced when co-cultured with CD8+ T-cells an average of 4.8-fold ($p<0.0001$) and 6.8-fold ($p<0.0001$) at 1:1 or 1:5 target:effector ratios, respectively, as compared to CD4+ T-cell monocultures. This transcriptional suppression occurred without reducing the frequency of HIV-infected cells. Comparison of transcriptional profiles revealed that co-cultured CD4+ T-cells adopted a resting phenotype, with downregulation of cell cycle, pro-inflammatory and apoptosis signaling. Pathways previously associated with HIV production were also downregulated, including oxidative phosphorylation and expression of mTOR targets. Of note, co-culture with CD8+ T-cells activated Wnt/β-catenin signaling and stem-cell memory pathways in HIV-infected memory CD4+ T-cells.
**Conclusion:** Our studies demonstrate that co-culture with CD8+ T-cells promotes changes in metabolic and cell survival pathways in memory CD4+ T-cells that may negatively regulate HIV expression and ultimately promote the establishment of latency. Modulation of this CD8-mediated activity may represent a tool to disrupt HIV latency and reservoir persistence in ART-treated individuals.

## 124 HIGH NEUTRALIZING CONVALESCENT PLASMA RESULTS IN RAPID CLEARANCE OF SARS-CoV-2

**Irene A. Abela**[1], Maddalena Marconato[2], Anthony Hauser[1], Magdalena Schwarzmüller[1], Dominique Braun[2], Selina Epp[1], Annette Audigé[1], Jacqueline Weber[1], Eméry Schindler[3], Michael Huber[1], Beat M. Frey[3], Roger Kouyos[2], Huldrych F. Günthard[2], Markus G. Manz[2], Alexandra Trkola[1]
*[1]University of Zurich, Zurich, Switzerland, [2]University Hospital Zurich, Zurich, Switzerland, [3]Blood Transfusion Service Zurich, Zurich, Switzerland*

**Background:** Neutralizing antibodies are recognized as a principal correlate for protection induced by SARS-CoV-2 vaccines and have been considered for antiviral treatment as an active component in convalescent plasma therapy (CPT) and as monoclonal antibody therapeutics. However, unless used at a very early stage of infection, antibody-based SARS-CoV-2 therapies have not achieved the substantial disease-modulating effect hoped for.
**Methods:** Here, we conducted a proof-of-principle study of CPT based on a phase I trial in thirty hospitalized COVID-19 patients with a median interval between the onset of symptoms and the first transfusion of 9 days (IQR, 7-11.8 days). A comprehensive longitudinal monitoring of the virologic, serologic, and disease status of recipients in conjunction with detailed post-hoc seroprofiling of transfused convalescent plasma allowed deciphering of parameters on which plasma therapy efficacy depends.
**Results:** In this study, CPT was safe as evidenced by the absence of transfusion-related adverse events. We also observed an overall low mortality (3.3%). Treatment with highly neutralizing plasma was significantly associated with faster virus clearance, as demonstrated by Kaplan-Meier analysis ($p = 0.034$) and confirmed in a parametric survival model including viral load and comorbidity (adjusted hazard ratio (HR) = 3.0 [95% confidence interval (CI) 1.1;8.1], $p = 0.026$) (Figure 1). Endogenous immunity had strong effects on virus

control. Lack of endogenous neutralizing activity at baseline was associated with a higher risk of systemic viremia. The onset of endogenous neutralization had a noticeable effect on viral clearance but, importantly, even after adjusting for their endogenous neutralization status recipients benefitted from plasma therapy with high neutralizing antibodies (HR= 4.0 [95% CI 1.3;13], p = 0.017).
**Conclusion:** In summary, our data demonstrate a clear impact of neutralizing antibody therapeutics on the rapid clearance of viremia and with this provide directions for improved efficacy evaluation of current and future SARS-CoV-2 therapies beyond antibody-based interventions. In particular, incorporating an assessment of the endogenous immune response and its dynamic interplay with viral production is critical for determining therapeutic effect.




## 125 SARS-CoV-2 ANTIBODY RESPONSES IN INDIVIDUALS FOLLOWING mRNA BOOSTER VACCINATION

Late Breaking

**Frauke Muecksch**[1], Zijun Wang[1], Alice Cho[1], Christian Gaebler[1], Victor Ramos[1], Tarek Ben Tanfous[1], Eva Bednarski[1], Justin Da Silva[1], Dennis Schaefer-Babajew[1], Irina Shiimeliovich[1], Anna Gazumyan[1], Marina Caskey[1], Paul Bieniasz[1], Theodora Hatziioannou[1], Michel Nussenzweig[1]
[1]*The Rockefeller University, New York, NY, USA*

**Background:** Two years after its onset, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains difficult to control despite the availability of several vaccines. Progress in controlling the pandemic is complicated by the emergence of variants with antibody-resistance.
**Methods:** Here we report on the evolution of antibody and memory B cell responses in a cohort of SARS-CoV-2 naïve individuals who received two doses of the Moderna (mRNA-1273) or Pfizer-BioNTech (BNT162b2) vaccines against SARS-CoV-2 and were boosted with a third mRNA vaccine dose thereafter.
**Results:** Plasma neutralizing antibody titers in individuals vaccinated with two mRNA vaccines doses decrease over time, but can be restored by a third, i.e., a booster dose. A third vaccine dose also results in dramatically increased plasma neutralizing activities against viral variants, including the delta and omicron variants. Boosting vaccinated individuals also increases the number of RBD-specific memory B cells, which display clonal turnover after the third dose of the vaccine. The mononclonal antibodies generated by those cells have greater somatic hypermutation and increased neutralizing activity when compared to antibodies generated after the second dose, indicative of continued evolution of the humoral response to SARS-CoV-2. A substantial fraction of the monoclonal antibodies isolated after the third dose of an mRNA vaccine are able to neutralize pseudoviruses representing the delta and omicron variants, at low antibody concentrations.
**Conclusion:** The data suggest that boosting vaccinated individuals with mRNA vaccines provides dramatically increased and broadened plasma neutralizing activity. This is the result of antibody evolution and the consequent production of potent and broadly active neutralizing antibodies.

## 126 HIV-1 RNA TRANSCRIPTS IN CSF CD4+ T CELLS, NOT MONOCYTES, ARE LINKED TO BRAIN INJURY

**Kazuo Suzuki**[1], John Zaunders[1], Thomas Gates[1], Angelique Levert[1], Shannen Butterly[1], Zhixin Liu[2], Takaomi Ishida[3], Chin-Shiou Huang[4], Caroline Rae[5], Lauriane Jugé[5], Lucette A. Cysique[6], Bruce Brew[1]
[1]*St Vincent's Hospital, Sydney, Australia,* [2]*University of New South Wales, Randwick, Australia,* [3]*DENKA Life Innovation Research Institute, Tokyo, Japan,* [4]*PlexBio Research Development, Taipei, Taiwan,* [5]*Neuroscience Research Australia, Randwick, Australia,* [6]*University of New South Wales, Sydney, Australia*

**Background:** Brain injury is prevalent in people with HIV-1 (PWH), despite suppressive ART. Our previous findings, using the highly sensitive Double-R assay, that high levels of cell-associated (CA) HIV-1 RNA transcripts in CSF cells correlated with current neuronal dysfunction, suggesting an active causal link. Monocytes (Mø) are widely considered the principal Trojan Horse by which HIV-1 enters and establishes brain infection. We hypothesized that Mø would be the chief source of transcripts.
**Methods:** CSF cells and PBMC from 16 PWH on fully suppressive ART were analyzed and accurately counted by 18-colour flow cytometry. Mø were highly purified from PBMC using magnetic beads and contained a median 0.3% contaminating CD4+ T cells. DNA and RNA were extracted from the samples of pelleted CSF cells, PBMC and purified blood Mø. CA HIV-1 RNA and DNA were determined by the Double-R πCode MicroDiscs assay, as copies/$10_6$ cells. In vivo brain injury was assessed with 1H MR spectroscopy.
**Results:** Pelleted CSF cells were 91% memory T cells, including median 3,605 CD4+ and 3,632 CD8 T cells, but only 378 Mø (>90% intermediate CD14+CD16+ phenotype). 14/16 and 13/16 samples of CSF cell samples had detectable CA HIV-1 RNA and HIV DNA. CA HIV-1 RNA transcripts in CSF numbered 9,226 copies/$10_6$ CD4+ T cells, compared to 185 copies/$10_6$ CD4+ T cells from PBMC. Importantly, CA HIV-1 RNA levels in CSF cells strongly correlated with their paired PBMC levels (r=0.83; p=0.003; Fig 1A). In contrast, even with >105 highly purified Mø from PBMC, only 6/16 samples contained detectable CA HIV-1 RNA transcripts, with a median of only 9 copies/$10_6$ Mø vs 306 copies/$10_6$ CD4+ T cells from the same PBMC samples, such that the contribution of Mø transcripts to PBMC was very minor (Fig1B). In CSF, CD4+ T cells were highly enriched with susceptible memory CXCR3+ CD49d+ integrinß7- cells (76% in CSF vs 18% in PBMC), CCR5+ cells (51% vs 28% in PBMC) and activated CD38+ and/or HLA-DR+ cells (18% vs 10%). Higher levels of CSF CA HIV-1 RNA transcripts were associated with greater brain injury in the FWM (Std β=-0.73; p<0.01) and PCC (Std β=-0.61; p<0.05).
**Conclusion:** Our results fundamentally challenge the monocyte-centered pathogenetic model of NeuroHIV in virally suppressed patients. Our results suggest a model where the residual infected memory CD4+ T cells in blood seed the brain through trafficking, with subsequent involvement of longer-lived resident brain macrophage lineage cells.

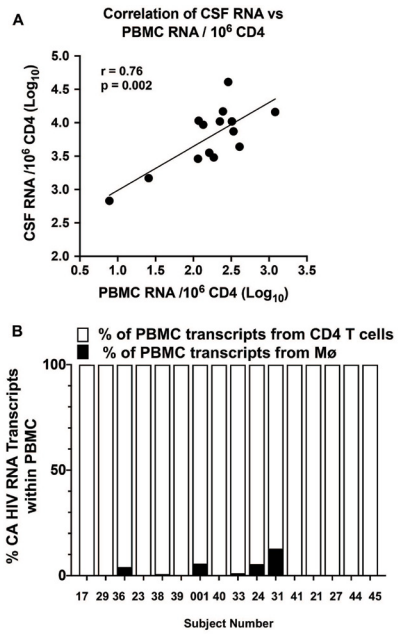



**Figure 1**
**A – Correlation between CA HIV RNA transcripts in CD4 in PBMC vs transcripts in CSF cells**
**B – Contribution of CD4 and Mø to HIV-1 RNA transcripts within PBMC**

## 127 PBR28 PET IMAGING IN PEOPLE WHO STARTED ART DURING ACUTE VERSUS CHRONIC HIV INFECTION

New Investigator Scholar

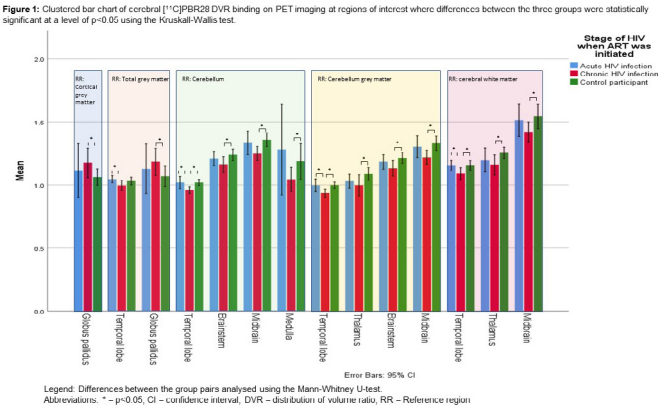
**Jasmini Alagaratnam**[1], Jaime Vera[2], Zhen Fan[3], John Thornhill[4], Jonathan Underwood[5], David Owen[6], Paul Edison[6], Sarah Fidler[6], Alan Winston[6]
*[1]Imperial College Healthcare NHS Trust, London, UK, [2]Brighton and Sussex Medical School, Brighton, UK, [3]Invicro, A Konika Minolta company, London, UK, [4]Queen Mary University of London, London, UK, [5]Cardiff University, Cardiff, UK, [6]Imperial College London, London, UK*

**Background:** Despite antiretroviral therapy (ART), persistent immune activation is described in people-with-HIV (PWH). Using translocator protein (TSPO) PET imaging, neuroinflammation is described in PWH on ART. Early ART initiation is associated with reduced markers of inflammation. We hypothesised that neuroinflammation, measured using TSPO [11C]PBR28, would be lower in PWH who initiated ART during acute (aPWH) versus chronic HIV infection (cPWH). We also investigate [11C]PBR28 binding normalised to reference regions previously used in TSPO studies.

**Methods:** Twenty TSPO high-affinity binders, neuro-asymptomatic PWH on virologically suppressive ART (9 aPWH, 11 cPWH) and 15 control participants underwent [11C]PBR28 PET scanning. Using a two-tissue compartment model, distribution volume ratios (DVR) were calculated using the reference regions: cortical grey matter (GM), total GM, cerebellum, cerebellar GM and cerebral white matter, at 20 regions of interest (ROIs). Differences in DVRs were compared between the groups using Kruskall-Wallis and Mann-Whitney U-tests.

**Results:** All PWH were male with median (interquartile range, IQR) age 40 (30, 46) and 45 (43, 52) years in the aPWH and cPWH, respectively, while 4/15 controls were female with median (IQR) age 26 (20, 59) years. Median (IQR) CD4 count (cells/μL) and CD4:CD8 were 687 (652, 1014) and 1.4 (1.2, 1.4), and 671 (470, 810) and 0.7 (0.6, 0.8) in aPWH and cPWH, respectively. Significant differences ($p<0.05$) in DVR were observed between cPWH and control participants and between cPWH and aPWH at certain ROIs (Figure 1). No differences in DVRs at any ROIs were noted between aPWH and controls. When utilising the cerebellum and cerebellar GM as reference regions, the greatest differences in DVR between the groups were observed and cPWH had lower binding at several ROIs.

**Conclusion:** Significant differences in [11C]PBR28 binding were identified between cPWH and control participants whereas differences between aPWH versus cPWH were observed less frequently. Neuroinflammation in aPWH and controls were similar, suggesting early ART initiation may mitigate neuroinflammatory responses. Cerebral [11C]PBR28 DVR binding is dependent on the reference region used and was lower in cPWH in several anatomical locations. We hypothesise this may be due to cerebral volume loss or regional neuroinflammation in cPWH. Urgent consensus is required on the optimal reference region in TSPO studies in PWH.




## 128 LONGITUDINAL MODELING OF EARLY HIV BURDEN IN THE CENTRAL NERVOUS SYSTEM

New Investigator Scholar

**Victor D. Armengol**[1], Veronika Shabanova[1], Lars Hagberg[2], Richard Price[3], Magnus Gisslen[2], Serena S. Spudich[1]
*[1]Yale University, New Haven, CT, USA, [2]Gothenburg University, Gothenburg, Sweden, [3]University of California San Francisco, San Francisco, CA, USA*

**Background:** The dynamics of plasma HIV replication during early infection including establishment of a viral set-point are well-known. However, the course of HIV in the central nervous system (CNS) after initial entry of HIV into this compartment is less understood. Using longitudinal samples, we modeled the natural history of HIV RNA in the cerebrospinal fluid (CSF) and plasma during early HIV prior to initiation of antiretroviral treatment (ART).

**Methods:** Participants with primary HIV infection (PHI, within 12 months of initial infection) were enrolled in prospective studies with paired longitudinal sampling of blood and CSF conducted in San Francisco, USA, and Gothenburg, Sweden prior to test-and-treat guidelines. This analysis incorporated all samples available over the first 3 years of infection from visits where participants were ART-naïve. HIV RNA assays had a lower limit of quantification of 40 copies/mL. Mean trajectory of CSF HIV RNA levels relative to time from infection was characterized using a restricted cubic spline function of time accounting for the correlated data within subjects. Parametric linear mixed effects models (LME) were also estimated to account for the covariate CD4/CD8 ratio and to confirm results from the spline analysis.

**Results:** The final analytical cohort included 110 PHI participants (95% male, median age = 37, days post infection = 91 at enrollment) with 228 CSF and 247 plasma measurements. The model shows an initial decrease in CSF HIV RNA over the first 100 days of estimated infection, after which CSF HIV RNA begins to increase at a slow rate (see Figure). Similar trends were seen in the plasma model, but at higher absolute values of HIV RNA copies/mL and with a narrower confidence interval compared to CSF. Plasma-CSF viral load difference declined rapidly in the first 100 days of infection. We confirmed the mean trajectory of change in HIV RNA derived from the cubic splines approach using the parametric LME model. Blood CD4/CD8 ratio negatively correlated with CSF HIV RNA, as there was a 0.69 unit decrease in $\log_{10}$ CSF HIV RNA for each unit increase in the CD4/CD8 ratio ($p = 0.0005$).

**Conclusion:** The viral dynamics in the CSF of ART-naïve individuals over the first 36 months of infection support the early spread of HIV to the CNS, and indicate that HIV replication is maintained in this compartment throughout the course of early infection prior to ART. Early initiation of ART may limit nervous system exposure to pathogenic effects of viral replication.

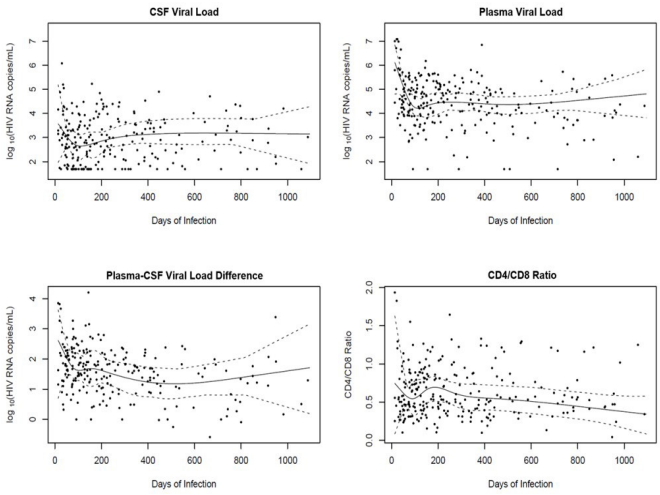



**Figure**. Trajectory models and individual data for HIV RNA dynamics in CSF and blood as well as CD4/CD8 ratio in blood over time. Dashed lines represent 95% confidence intervals.

## 129 CD4+ DEPLETION RESULTS IN ROBUST CNS REBOUND AND LARGER MACROPHAGE RESERVOIRS

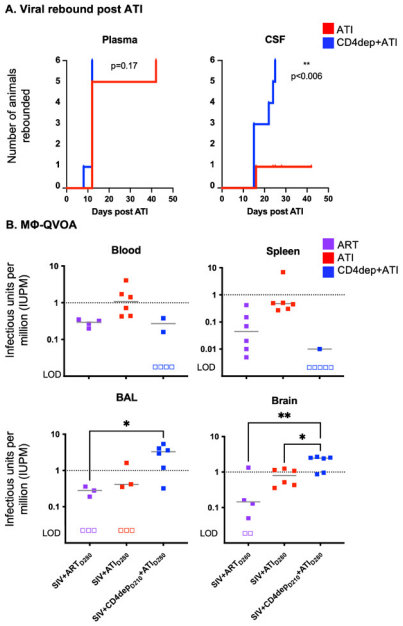
**Rebecca T. Veenhuis**[1], Celina Abreu[1], Edna Ferreira[1], Janaysha Ratliff[1], Suzanne Queen[1], Erin Shirk[1], Joseph Mankowski[1], Lucio Gama[1], Janice Clements[1]
[1]*The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** Macrophages (MΦ) are important drivers of HIV pathogenesis and progression to AIDS. The significance of MΦ infection in viremic individuals is well established, in contrast to the role of MΦ in suppressed HIV infection. Contribution of the MΦ reservoir to viral reactivation and rebound upon analytical treatment interruption (ATI) of antiretroviral therapy (ART) has not been determined. Using an SIV/rhesus macaque model of HIV, we sought to determine whether depleting CD4 T cells from blood and tissue altered the contribution of the MΦ reservoir to viral rebound.

**Methods:** In the SIVmac251 model, we assessed the effect of CD4 depletion on MΦ reservoirs in blood, spleen, bronchoalveolar lavage (BAL) and brain. Three groups were assessed (n=18). All animals began ART treatment at 14 days post infection (dpi), and continued until 280dpi, the terminal timepoint for the ART group. At 280dpi the ATI group was withdrawn from ART. At 210dpi, the CD4dep+ATI group was given an anti-CD4 antibody (CD4R1) intravenously to deplete CD4 T cells from blood and tissue. At 280dpi this group was also withdrawn from ART for ATI. Terminal time points for both ATI groups were determined when plasma viral rebound reached set-point. To assess the MΦ latent reservoir, we utilized the IPDA and MΦ-QVOA.

**Results:** All animals had similar acute viral loads and suppressed within 40 days of ART initiation. We observed significant CD4 depletion in the blood (95%), lymph nodes (70%) and spleen (50%) post CD4R1 administration, which was maintained throughout ATI. No difference was observed in time-to or set-point of viral rebound in the plasma in the ATI groups. In contrast, only 1/6 animals in the ATI group rebounded in CSF compared to all 6/6 animals in CD4dep+ATI group. We observed no change in the intact DNA reservoir in MΦ isolated from blood, spleen and BAL. However, there was a significant increase in the reactivatable reservoir in MΦ-rich tissues (brain and BAL) in CD4dep+ATI compared to ATI and ART groups. In contrast, MΦ isolated from CD4-rich tissues (blood and spleen) had smaller reactivatable reservoirs.

**Conclusion:** Our data demonstrate that CD4 depletion prior to ATI does not reduce the viral reservoir and enhances reactivation of latently-infected MΦ. Our model closely mimics what is observed in late-stage infection, as CD4 T cells are depleted, and infected MΦ become the principal reservoir driving viremia. This work has implications for cure, as eliminating CD4 T cells could result in severe disease outcomes post ATI.




## 130 NEUROSYMPTOMATIC HIV-1 CSF ESCAPE ASSOCIATES WITH REPLICATION IN CNS CD4+ T CELLS

**Laura Kincer**[1], Ameet N. Dravid[2], Paola Cinque[3], Mattia Trunfio[4], Andrea Calcagno[4], Serena S. Spudich[5], Magnus Gisslen[6], Richard Price[7], Sarah B. Joseph[1]
[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC, USA,* [2]*Poona Hospital and Research Center, Pune, India,* [3]*San Raffaele Scientific Institute, Milan, Italy,* [4]*University of Turin, Turin, Italy,* [5]*Yale University, New Haven, CT, USA,* [6]*University of Gothenburg, Gothenburg, Sweden,* [7]*University of California San Francisco, San Francisco, CA, USA*

**Background:** Neurosymptomatic (NS) cerebrospinal fluid (CSF) escape occurs in people living with HIV-1 who present with neurologic symptoms and have elevated HIV-1 RNA in their CSF despite being on antiretroviral therapy (ART) and having undetectable or low levels of HIV-1 RNA in the blood. The cellular source of NS escape virus is unknown.

**Methods:** We examined viral populations in blood plasma and CSF from people with NS CSF escape (neurologic symptoms with CSF viral load (VL) >40 copies/ml, and CSF VL > plasma VL, n=36). We used single genome amplification (SGA) and/or Illumina MiSeq deep sequencing with Primer ID to asses genetic diversity in partial env sequences (V1-V3) and drug resistance in PR, RT, and IN. Full-length env genes were cloned from the CSF of 10 participants and their ability to enter cells expressing a low density of CD4 (a predictor of macrophage tropism) was assessed. Pairwise distances of partial envs were calculated.

**Results:** Median CSF and plasma VLs were 2,400 and 140 copies/ml, respectively. The median blood CD4 count was 471 cells/ul, nadir CD4 count 98 cells/ul, and CSF white blood cells (WBC) 21 cells/ul. CSF NS escape populations either had one major lineage (47%), two major lineages (33%) or a highly diverse, recombinant population (16%). Participants with the most diverse populations also had lower nadir CD4 counts compared to those with single lineages (t test, p = 0.04). 97% of escape populations were at least partially resistant to their ART regimen and, of those, 94% saw symptoms improve after ART optimization. All escape viruses examined (N=25 from 10 participants) were T cell-tropic.

**Conclusion:** Observed genetic diversity, drug resistance and resolution of symptoms after ART optimization indicate that NS escape is produced by replication of partially drug resistant virus in the CNS of ART-treated participants. In addition, profound immunosuppression prior to ART was associated with escape populations with higher genetic diversity likely due to persistent replication in the CNS of these participants. The escape viruses remaining T cell-tropic despite replication and evolution in the CNS suggests that they primarily replicate in CD4+ T cells. Together these results illustrate that NS escape populations are produced by replication of partially drug resistant viruses in the CNS and suggest that evolution of escape virus is facilitated by elevated CSF WBCs and an impaired ability of the immune system to control viral replication.

## 131 SARS-CoV-2 CSF N-ANTIGEN DETECTION IS ASSOCIATED WITH CNS INFLAMMATION IN NEUROCOVID

**Arvid Eden**[1], Anna Grahn[1], Daniel Bremell[1], Pradeepthi Bathala[2], Dietmar Fuchs[3], Johanna Gostner[4], Salvia Mishagian[2], Navaratnam Manjula[2], Staffan Nilsson[1], Michael Schöll1, George Sigal[2], Erika Stentoft[1], Martin Stengelin[2], Henrik Zetterberg[1], Magnus Gisslen[1]

*[1]Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden, [2]Meso Scale Diagnostics, LLC, Rockville, MD, USA, [3]Institute of Biological Chemistry, Medical University of Innsbruck, Biocenter, Innsbruck, Austria, [4]Institute of Medical Biological Chemistry, Medical University of Innsbruck, Biocenter, Innsbruck, Austria*

**Background:** The underlying CNS pathogenesis in COVID-19 is not clear and viral RNA is rarely detected in cerebrospinal fluid (CSF). We measured viral antigen and biomarker profiles in CSF in relation to neurological symptoms and disease severity.

**Methods:** We included 44 (32% female) hospitalized patients (26 moderate, 18 severe COVID-19) and 10 healthy controls (HC). 21 patients were neuroasymptomatic (NA), 23 neurosymptomatic (NS; encephalopathy=21, encephalitis=1, GBS=1). For antigen and cytokine analyses, a patient control (PC; n=41) group (COVID-negative with no sign of CNS infection in clinical CSF samples) was used. CSF nucleocapsid antigen (N-Ag) was analyzed using an ultrasensitive antigen capture immunoassay platform, S-PLEX direct detection assay, S-PLEX SARS-CoV-2 N Kit (MesoScale Diagnostics, LLC. Rockville, MD). Additional analyses included CSF neopterin, β2-microglobulin, cytokines and neurofilament light (NfL).

**Results:** CSF N-Ag was detected in 31/35 patients (0/41 controls) while viral RNA was negative in all. CSF N-Ag was significantly correlated with CSF neopterin (r=0.38; p=0.03) and IFN-γ (r=0.42; p=0.01) adjusted for sampling day. No differences in CSF N-Ag concentrations were found between patient groups. All patient groups had markedly increased CSF neopterin, β2M, IL-6, IL-10 and TNF-α compared to controls, while IL-2, IL-1β and IFN-γ were significantly increased only in the NS group. CSF biomarkers were associated with time from symptom onset to CSF sampling. After adjusting for time of sampling, the NS group had significantly higher CSF IFN-γ (p=0.03), and showed a statistical trend towards significantly higher CSF neopterin, IL-6 and TNF-α (p=0.056-0.06) than the NA group. Additionally, age-adjusted CSF NfL was higher in the NS compared to the HC (p=0.01) group. No differences were seen in any CSF biomarkers in moderate compared to severe disease.

**Conclusion:** Viral antigen is detectable in CSF in a majority of patients with COVID-19 despite the absence of detectable viral RNA, and is correlated to CNS immune activation markers. Patients with neurological symptoms had a more marked immune activation profile compared to NA patients, as well as signs of neuroaxonal injury compared to controls. These observations could not be attributed to a difference in COVID-19 severity. Our results highlight the importance of neurological symptoms and indicate that the CNS immune response and CNS pathogenesis can be initiated by viral components without direct viral invasion of the CNS.

## 132 IS THERE A ROLE OF NOVEL ART REGIMENS IN THE DECLINING PREVALENCE OF HAND?

New Investigator Scholar

**Ilaria Mastrorosa**[1], Anna Clelia Brita[1], Annalisa Mondi[1], Giulia Del Duca[1], Patrizia Lorenzini[1], Alessandra Vergori[1], Valentina Mazzotta[1], Roberta Gagliardini[1], Marta Camici[1], Rita Bellagamba[1], Federico De Zottis[1], Marisa Fusto[1], Stefania Cicalini[1], Andrea Antinori[1], Carmela Pinnetti[1]

*[1]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy*

**Background:** HIV-associated neurocognitive disorder (HAND) is still prevalent among people living with HIV (PLWH). The aim of the study was to evaluate prevalence and predictors of HAND, including treatment related factors, in a large cohort of PLWH over the last decade.

**Methods:** Monocentric, retrospective, cross-sectional analysis of neurocognitive profile in antiretroviral therapy (ART)-treated PLWH, prospectively enrolled between 2009-2020. All patients (pts) underwent neuropsychological assessment (NPA) by a standardized battery of 13 tests on 5 different domains and were classified as having HAND according to Frascati's criteria. Pts were defined complaining or not-complaining if a deficit of memory, attention or concentration was or not reported. Chi-square test for trend was employed to compare prevalence overtime. A multivariable logistic regression model was fitted to investigate predictors of HAND.

**Results:** A total of 2,383 NP consecutive tests over 1,365 PLWH was collected during 4 time periods (2009-2011,2012-2014,2015-2017,2018-2020). Main characteristics at NPA were: male 82%, MSM 45%, HCVAb+ 22%, median (IQR) of 10 (4-20) years of infection and 13 (8-14) of education; HIV-RNA <40 cp/mL in 85%, median CD4+of 600 (419-790) cell/mm$_3$, nadir CD4+<200 cell/mm$_3$ in 35%; 42% of pts were receiving NRTI+NNRTI, 19% NRTI+bPI, 18% NRTI+InSTI, 8% a dual regimen (4% InSTI-based); 8% of pts received dolutegravir. In overall population, HAND prevalence was 22%: ANI 16%, MND 5.5%, HAD 1%. In 791/2,383 (33%) tests a cognitive complaint was reported and HAND prevalence was 40%, higher than among not-complaining (13%). Over the study period, a decreasing frequency of HAND was found in the entire population (Tab.1). Factors associated to HAND were older age, lower educational level, lower current CD4+count and HCV co-infection. Compared to pts receiving a NNRTI, those receiving dual and InSTI-based therapies were associated to a decreased risk of having HAND. To be tested in more recent years significantly predicted a reduced risk of HAND (Tab.2).

**Conclusion:** In this large cohort of ART-treated PLWH, mostly virologically suppressed, we observed a clear decrease in HAND prevalence over the last decade. Besides HIV-related factors and patient characteristics, the reduced risk of HAND observed with dual and InSTI-based regimens along with a more recent initiation of ART, could suggest a potential role of new treatment strategies in this decline, due to their greater virological efficacy and better tolerability.

| | *Complaining patients (791 tests)* | *Not-complaining patients (1,592 tests)* | *All study population (2,383 tests)* |
|---|---|---|---|
| *HAND* | 316 (40.0%) | 209 (13.1%) | 525 (22.0%) |
| *ANI* | 192 (24.3%) | 181 (11.4%) | 373 (15.6%) |
| *MND* | 105 (13.3%) | 26 (1.6%) | 131 (5.5%) |
| *HAD* | 19 (2.4%) | 2 (0.1%) | 21 (0.9%) |
| *HAND prevalence according to calendar period* | | | |
| *2009/2011* | 74/142 (52.1%) | 34/145 (23.4%) | 108/287(37.6%) |
| *2012/2014* | 117/257 (45.5%) | 65/482 (13.5%) | 182/739 (24.6%) |
| *2015/2017* | 68/192 (35.4%) | 42/366 (11.5%) | 110/558 (19.7%) |
| *2018/2020* | 57/200 (28.5%) | 68/599 (11.3%) | 125/799 (15.6%) |
| *p at chi square for trend* | *< 0.001* | *0.002* | *<0.001* |

**Table 1. HAND prevalence by calendar periods, according to cognitive complaint.** *Abbreviations: ANI, Asymptomatic Neurocognitive Impairment; MND, Mild Neurocognitive Disorder; HAD, HIV-Associated Dementia; HAND, HIV-associated neurocognitive disorder.*

**Table 2. HAND predictors by multivariable logistic regression.** *Adjusted for: gender, mode of HIV transmission (homo/heterosexual, intravenous drug users), years from HIV test, nadir CD4$^+$ (< or ≥ 200 cells/mm$^3$), HIV-RNA at NPA (< or ≥ 40 cp/mL).*

| | *AOR* | *95% CI* | | *p-value* |
|---|---|---|---|---|
| Age, 10 years increase | 1,16 | 1,03 | 1,30 | 0,013 |
| CD4$^+$ at NPA (cells/mm$^3$) *< 350* | 1,00 | | | |
| *351-500* | 0,66 | 0,46 | 0,95 | 0,025 |
| *501/700* | 0,50 | 0,36 | 0,71 | 0,000 |
| *> 700* | 0,45 | 0,31 | 0,64 | 0,000 |
| Education (per 1 year more) | 0,84 | 0,81 | 0,86 | 0,000 |
| HCV *seronegative* | 1,00 | | | |
| *HCV seropositive* | 1,44 | 1,09 | 1,92 | 0,011 |
| Type of current ART regimen | | | | |
| *NRTI+NNRTI* | 1,00 | | | |
| *NRTI+bPI* | 1,15 | 0,85 | 1,55 | 0,376 |
| *NRTI+INSTI* | 0,67 | 0,46 | 0,97 | 0,035 |
| *dual therapy* | 0,59 | 0,38 | 0,93 | 0,024 |
| *bPI monotherapy* | 0,74 | 0,44 | 1,23 | 0,242 |
| Years of NPA | | | | |
| *2009-2011* | 1,00 | | | |
| *2012-2014* | 0,73 | 0,52 | 1,02 | 0,067 |
| *2015-2017* | 0,48 | 0,33 | 0,70 | 0,000 |
| *2018-2020* | 0,43 | 0,29 | 0,63 | 0,000 |
| Complaining | 3,83 | 3,01 | 4,86 | 0,000 |

## 133 ACTG A5324: A RANDOMIZED TRIAL OF ART INTENSIFICATION FOR COGNITIVE IMPAIRMENT IN PWH

**Scott L. Letendre**[1], Jhoanna Roa[2], Huichao Chen[3], Ashley McKhann[3], Christina M. Marra[4], Eric S. Daar[5], Peter W. Hunt[6], Thomas Campbell[7], Shobha Swaminathan[8], Belinda Ha[9], Beverly Alston-Smith[10], Robert Paul[11], Serena S. Spudich[12]

*[1]University of California San Diego, San Diego, CA, USA, [2]DLH Corporation, Silver Spring, MD, USA, [3]Harvard TH Chan School of Public Health, Boston, MA, USA, [4]University of Washington, Seattle, WA, USA, [5]University of California Los Angeles, Los Angeles, CA, USA, [6]University of California San Francisco, San Francisco, CA, USA, [7]University of Colorado Denver, Denver, CO, USA, [8]Rutgers University, Newark, NJ, USA, [9]ViiV Healthcare, Research Triangle Park, NC, USA, [10]Division of AIDS, NIH, Rockville, MD, USA, [11]University of Missouri St Louis, St Louis, MO, USA, [12]Yale University, New Haven, CT, USA*

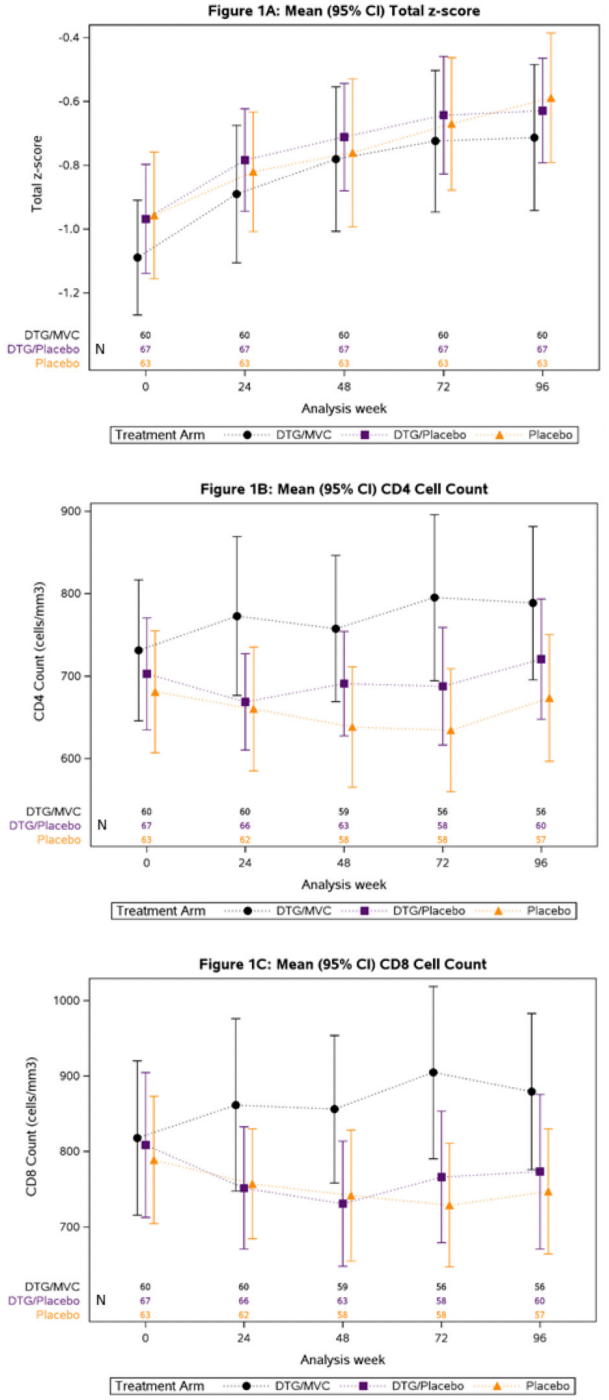
**Background:** Cognitive impairment in people with HIV (PWH) on antiretroviral therapy (ART) may result from HIV persistence in the central nervous system. A5324 was a randomized double-blind placebo controlled trial to test whether ART intensification would improve neuropsychological (NP) performance in PWH with neurocognitive impairment on suppressive ART.

**Methods:** PWH with plasma HIV RNA <50 cps/ml on ART not containing integrase inhibitors or maraviroc (MVC) were eligible if they performed >1 SD below the normative mean on two NP tests in different domains out of a total of 14 (US sites) or 11 (international sites), without other causes of impairment. Participants were randomized to add dolutegravir (DTG)+ MVC, DTG+ placebo, or dual placebo, then repeated NP testing at weeks 24, 48, 72, and 96. Blood CD4+ and CD8+ T-cells, the Beck Depression Inventory-II (BDI-II), and the Patient Health Questionnaire 9 (PHQ-9) were measured at each visit. The primary outcome was the change from baseline to week 48 on the normalized total z-score, which was the average of the individual test z-scores.

**Results:** Of 357 screened, 191 were enrolled (82% from US); 71% male, gender information unavailable, 51% black, 36% white, and 22% Hispanic ethnicity; median age 53 (IQR 47-57) years; median CD4+ T-cells 683 (464-886) cells/mm$_3$. Foremost reason for screen failure was unimpaired NP (29%). 35% met Frascati criteria for asymptomatic neurocognitive impairment, 56% for mild neurocognitive disorder, and 9% for HIV-associated dementia. Study drug was discontinued due to adverse event in 15 (8%), with no difference between arms in time to discontinuation (p=0.17). Total z-score improved over time and change from baseline did not differ between arms at week 48 or other timepoints (Figure 1A). BDI-II and PHQ-9 scores remained stable over time, with no differences between treatment arms. Participants randomized to DTG+MVC exhibited a greater increase in CD4+ and CD8+ T-cells than those in the placebo or DTG arms (p<0.05, Figure 1B & C). Sex, race, study site, or adjustment for baseline z-score did not influence the results.

**Conclusion:** Compared to placebo, ART intensification with DTG or DTG+MVC did not alter NP performance or depressive symptoms over time in PWH with cognitive impairment. Participants who received DTG+MVC had greater increases in CD4+ and CD8+T-cells than those in the other arms. The trial result does not support empiric ART intensification as a treatment for cognitive impairment in PWH on suppressive ART.

**Figure 1.** Total z-score, CD4+ and CD8+ T-cell measurements through week 96 of follow-up.




## 134 IMPROVING INTESTINAL BARRIER USING GLP-2 AGONIST REDUCES ARTERIAL INFLAMMATION IN PWH

Late Breaking

**Caroline E. Diggins**[1], Shibani Mukerji[1], Douglas S. Kwon[2], Charles F. Saylor[1], Lediya Cheru[1], Jae Sim[1], Meaghan Flagg[2], Bjoern Corleis[2], Emily Rudmann[1], Shady Abohashem1, Ahmed Tawakol[1], Janet Lo[1]

*[1]Massachusetts General Hospital, Boston, MA, USA, [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA*

**Background:** Arterial inflammation, a predictor of cardiovascular events, is greater in people with HIV (PWH) and is related to plaque macrophage content, but the mechanisms driving this elevation are not clear. The intestinal mucosal barrier is impaired in PWH and residual inflammation continues despite HIV RNA suppression with ART. We hypothesized restoration of the intestinal epithelial barrier using the intestinal-specific trophic factor, glucagon-like peptide 2

(GLP-2) agonist, teduglutide would reduce proinflammatory immune cells and arterial inflammation.

**Methods:** In a randomized, double-blind, placebo-controlled study, 28 PWH on ART with suppressed HIV RNA were randomized to teduglutide or placebo for 6 months. 20 participants completed the intervention. Arterial inflammation was assessed at baseline and end of study by 18-fluorodeoxyglucose (FDG)-PET/CT. PBMCs were collected for flow cytometric analysis. Targeted metabolites were assessed in plasma by LC-MS/MS.

**Results:** Compared to placebo, teduglutide decreased the target-to-background ratio (TBR) of the most-diseased segment (MDS) of the carotid index vessel (left or right carotid artery with higher baseline TBR) by 0.39 (p=0.01 ANCOVA). % Reduction in TBR of the left carotid MDS was greater with teduglutide vs. placebo (-15.44 ± 7.49% vs. +5.55 ± 5.30%, p=0.04). Activated monocyte and CD8+ T-cells decreased with teduglutide vs. placebo (%CD14+CD86+CD40+ of CD14+ monocytes, -19.24 ± 5.31 vs. -3.31 ± 4.96, p<0.05; %HLA-DR+CD38+ CD8 cells of CD3+ cells, -0.33 ± 0.39 vs. +0.67 ± 0.33, p<0.05). Kynurenic acid (KA), an anti-inflammatory intermediate metabolite of kynurenine, trended to increase with teduglutide vs. placebo (9.46 ± 5.62 nM vs. -4.79 ± 5.03 nM, p=0.07 for log2 mean-normalized values). Change in carotid index vessel MDS TBR correlated positively with changes in CD14+CD86+CD40+ monocytes (r=0.55, p<0.05) and HLA-DR+CD38+ CD8 cells (r=0.55, p=0.03) and inversely with KA (r=-0.58, p=0.02).

**Conclusion:** Amelioration of the intestinal epithelial barrier with teduglutide decreased arterial inflammation, activated monocytes, and CD8+ T-cells. Teduglutide-treated participants also showed increase in plasma KA, a metabolite with anti-inflammatory effects. This proof-of-concept study provides support for future research investigating intestinal epithelial integrity as a target for reduction of immune activation and cardiovascular disease in PWH.

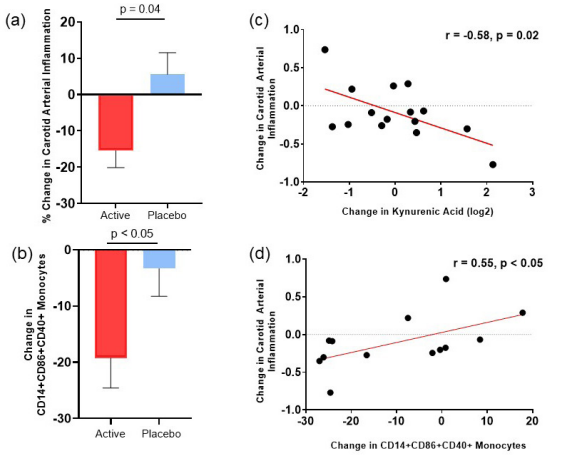



**Figure.** Cardiovascular inflammation and monocyte activation decline with teduglutide treatment. (a) % change in TBR of the left carotid artery MDS between baseline and study end. (b) Absolute change in CD14+CD86+CD40+ activated monocytes as a % of CD14+ cells. Reductions in arterial inflammation (TBR) of the carotid index vessel MDS correlated with (c) increases in circulating kynurenic acid levels and (d) reductions in activated monocytes in full cohort. Bar graphs show mean ± standard error.

## 135 DOLUTEGRAVIR WITH RECYCLED nRTIs IS NONINFERIOR TO PI-BASED ART: VISEND TRIAL

**Lloyd B. Mulenga**[1], Sombo Fwoloshi[1], Aggrey Mweemba[1], Mpanji Siwingwa[1], Suilanji Sivile[1], Davies Kampamba[2], Danielle C. Engamba[1], Nyuma Mbewe[1], Henry Phiri[2], Aaron Shibemba[1], Bryony Simons[3], C. William Wester[4], Lameck Chirwa[1], Andrew Hill[5]

*[1]University Teaching Hospital, Lusaka, Zambia, [2]Government of Zambia Ministry of Health, Lusaka, Zambia, [3]London School of Economics & Political Science, London, UK, [4]Vanderbilt University, Nashville, TN, USA, [5]University of Liverpool, Liverpool, UK*

**Background:** The WHO has recommended a rapid transition from non-nucleoside reverse transcriptase inhibitors (NNRTI)-based to dolutegravir (DTG)-based ART regimens due to a rise in HIV drug resistance to NNRTIs. However, there is a paucity of data to inform transition of individuals not virologically suppressed on NNRTI-based to DTG-based regimens while maintaining the NRTI backbone.

**Methods:** We conducted a 144 week, randomized, open-label, Phase III noninferiority trial in Zambia where we randomized adults on tenofovir disoproxil fumarate (TDF), lamivudine (3TC) plus efavirenz (EFV) or nevirapine (NVP). In Arm A, adults with viral load (VL) <1,000 copies/mL were randomized to TDF, 3TC, DTG (TLD) or tenofovir alafenamide (TAF), emtricitabine (FTC), DTG (TAFED). In Arm B, those with VL 1000 copies/mL were randomized to TLD, TAFED, or the standard-of-care (SOC) second line protease inhibitor (PI/r)-based regimen lopinavir/ritonavir (LPV/r) or atazanavir/r (ATV/r), zidovudine (ZDV), 3TC. Primary end point was VL <1,000 copies /mL (viral suppression (VS)) at week 48, assessed using the FDA snapshot algorithm (intent-to-treat (ITT) population). Noninferiority was tested with a margin of 10 percentage points. We herein report the primary (week 48) efficacy data.

**Results:** Of 1201 randomized adults, 100% were black, 61% female, with a median age of 40 years. At week 48, in Arm A, 88% TLD-treated adults maintained VS compared to 87% for TAFED [difference, -0.5%, 95% CI -6.9 - 5.9]. In Arm B, 82% TLD-treated adults achieved VS, compared to 87% for TAFED and 76% for 3TC/ZDV/PI/r. Noninferiority of switching to both DTG-based arms was achieved compared to the SOC boosted PI regimen [TLD versus ZDV/3TC/PI/r difference, 6.2% [-0.7 - 13.0]; TAFED versus ZDV/3TC/PI/r difference, 11.7% [5.3 - 18.0]. Consistent results were shown in other analyses (Table 1). Weight gain was greater among females receiving TAFED (mean increase, +4.8kg in TAFED, +2.8kg in TLD, +2.4kg in ZDV/3TC/PI/r groups) but was similar among males (mean increase, +2.9kg in TAFED, +2.6kg in the TLD, +2.7kg in ZDV/3TC/PI/r groups).

**Conclusion:** In the VISEND trial, HIV-positive adults with virologic failure to TDF/3TC/NNRTI, had favorable outcomes when switched to DTG with either TAF/FTC or TDF/3TC compared to those switched to SOC boosted-PI ART. Women receiving DTG, however, due to significant weight gain, may be at heightened risk for non-communicable diseases and/or metabolic complications hence longer-term follow up is needed.

*Table 1: Virological efficacy at Week 48 by study arms*

| | Arm A: HIV RNA <1,000 cp/mL | | Arm B: HIV RNA ≥ 1,000 cp/mL | | |
|---|---|---|---|---|---|
| | TDF/3TC/DTG (TLD) | TAF/FTC/DTG (TAFED) | TDF/3TC/DTG (TLD) | TAF/FTC/DTG (TAFED) | ZDV/3TC/PI/r |
| | (n=209) | (n=209) | (n=208) | (n=211) | (n=364) |
| **HIV RNA results (Week 48)** | | | | | |
| n/total (%) | | | | | |
| <50 cp/mL (Observed) | 168/187 (90) | 161/186 (87) | 148/182 (81) | 172/193 (89) | 231/314 (74) |
| <50 cp/mL (ITT) | 168/209 (80) | 161/209 (77) | 148/208 (71) | 172/211 (82) | 231/364 (63) |
| <1000 cp/mL (Observed) | 183/187 (98) | 182/186 (98) | 170/182 (93) | 184/193 (95) | 275/314 (88) |
| <1000 cp/mL (ITT) | 183/209 (88) | 182/209 (87) | 170/208 (82) | 184/211 (87) | 275/364 (76) |

## 136 A RANDOMIZED TRIAL OF SWITCHING TREATMENT-EXPERIENCED ADULTS FROM PI/r TO DTG

**Loice A. Ombajo**[1], Jeremy Penner[2], Joseph Nkuranga[1], Jared Mecha[1], Margaret Mburu[1], Collins Odhiambo[1], Florentius Ndinya[3], Rukia Aksam[3], Richard Njenga[4], Simon Wahome[4], Peter Muiruri[4], Catherine Ngugi[5], Anton Pozniak[6]

*[1]University of Nairobi, Nairobi, Kenya, [2]University of British Columbia, Vancouver, Canada, [3]Jaramogi Oginga Odinga Teaching & Referral Hospital, Kisumu, Kenya, [4]Kenyatta National Hospital, Nairobi, Kenya, [5]National AIDS and STD Control Programme, Nairobi, Kenya, [6]Chelsea and Westminster Hospital, London, UK*

**Background:** Dolutegravir (DTG) has shown good efficacy and tolerability among treatment-experienced adults with HIV. Most HIV-infected adults in Kenya with prior non-nucleoside reverse transcriptase inhibitor (NNRTI) failure are on ritonavir-boosted protease inhibitor (PI/r)-based second line regimens. We evaluated the efficacy and safety of switching virally suppressed adults from a second-line PI/r-containing regimen to a DTG-containing regimen, without prior drug resistance testing.

**Methods:** The Second-line Switch to DTG (2SD) study is an open-label, randomized, active-controlled, non-inferiority trial conducted at four sites in Kenya. Eligible participants were HIV-1 infected adults (≥ 18 years) who were virally suppressed (plasma HIV RNA < 50 copies/mL) for at least 12 weeks prior to enrolment and on a second-line regimen of PI/r + 2 nucleoside reverse transcriptase inhibitors (NRTIs) for at least 24 weeks, and without prior integrase inhibitor exposure. Participants were randomized (1:1) to switch to DTG or continue their pre-enrollment PI/r; pre-enrollment NRTIs continued in both arms. The primary endpoint was proportion of participants with plasma HIV-1 RNA of ≥ 50 copies/mL at week 48 in the intention-to-treat-exposed (ITT-E) population using the FDA snapshot algorithm and a non-inferiority margin of 4%.

**Results:** Between Feb 10 and Sep 3, 2020, 795 participants were randomized and 791 were treated (397 DTG, 394 PI/r) and included in ITT-E analysis. All participants were black and 524 (66%) were female, with baseline characteristics balanced between arms. At week 48, the proportion of participants with HIV-1 RNA ≥ 50 copies/mL was 5.0% (20/397) in the DTG arm and 5.1% (20/394) in the PI/r arm (treatment difference [95% confidence interval], -0.04% [-3.09 to 3.02]), meeting non-inferiority criteria (Table 1). No participants with protocol-defined virological failure had detectable genotypic resistance to the study drug at time of failure in either arm. Treatment-related adverse events (AE) occurred in 88 (23%) participants on DTG and 76 (20%) participants on PI/r; treatment-related grade 3 or 4 AEs were similar (6.0% on DTG; 7.1% on PI/r), with no treatment-related serious AEs in either arm. Participants discontinuing study drug due to any AE was 1 (0.3%) on DTG and 3 (0.8%) on PI/r.

**Conclusion:** Switching from PI/r to DTG may be an effective and safe strategy for treatment-experienced virally suppressed adults with no prior InSTI-exposure, even without knowledge of prior resistance.

Table 1: Primary virologic outcomes at week 48

| | DTG group (n=397) | PI/r group (n=394) | Total (n=791) | Difference (95% CI); p value |
|---|---|---|---|---|
| **HIV-1 RNA ≥ 50 copies/mL** | **20 (5.0%)** | **20 (5.1%)** | **40 (5.1%)** | **-0.04% (-3.09 – 3.02); 0.98** |
| HIV-1 RNA ≥ 50 copies/mL in week 48 window | 5 (1.3%) | 6 (1.5%) | 11 (1.4%) | |
| Treatment discontinued before week 48 due to lack of efficacy | 15 (3.8%) | 14 (3.6%) | 29 (3.7%) | |
| **No virological data available** | **18 (4.5%)** | **12 (3.0%)** | **30 (3.8%)** | |
| Discontinued because of AE/death with last available HIV-1 RNA <50 copies/mL | 5 (1.3%) | 5 (1.3%) | 10 (1.3%) | |
| Discontinued for other reasons with last available HIV-1 RNA <50 copies/mL | 10 (2.5%) | 5 (1.3%) | 15 (1.9%) | |
| On study drug but missing VL data in the week 48 window | 3 (0.8%) | 2 (5.1%) | 5 (0.6%) | |
| **HIV-1 RNA < 50 copies/mL in week 48 window** | **359 (90.4%)** | **362 (91.9%)** | **721 (91.2%)** | **-1.45% (-5.41 – 2.51); 0.47** |

Data are n (%) unless otherwise stated. Abbreviations: AE, adverse event; DTG, dolutegravir; HIV-1, human immunodeficiency virus type 1; PI/r, ritonavir-boosted protease inhibitor; VL, viral load.

## 137 NUCLEOSIDES AND DARUNAVIR/DOLUTEGRAVIR IN AFRICA (NADIA) TRIAL: OUTCOMES AT 96 WEEKS

Late Breaking

**Nicholas Paton**[1], Joseph Musaazi[2], Cissy Kityo[3], Stephen I. Walimbwa[2], Apolo Balyegisawa[2], Anne Hoppe[2], Arvind Kaimal[2], Grace Mirembe4, Gilbert Ategeka[5], Henry Mugerwa[3], Margaret Borok[6], Abraham Siika[7], Barbara Castelnuovo[2], Andrew D. Kambugu[2]

*[1]National University of Singapore, Singapore, Singapore, [2]Infectious Diseases Institute, Kampala, Uganda, [3]Joint Clinical Research Centre, Lubowa, Uganda, [4]Makerere University Walter Reed Project, Kampala, Uganda, [5]Joint Clinical Research Centre, Fort Portal, Uganda, [6]University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe, [7]Moi University School of Medicine, Eldoret, Kenya*

**Background:** At 48 weeks, the NADIA trial found non-inferiority of dolutegravir versus darunavir and non-inferiority of maintaining tenofovir versus switching to zidovudine in second-line therapy. WHO guidelines continue to recommend a switch to zidovudine. We report new follow-up data to end of trial at week 96.

**Methods:** Patients failing NNRTI/tenofovir/lamivudine first-line with confirmed VL ≥1000 copies/ml were randomised to receive dolutegravir or ritonavir-boosted darunavir; and to receive tenofovir or zidovudine, all with lamivudine. Treatment was monitored by open VL at 24, 48 and 96 weeks (and 72 weeks, if unstable) following WHO guidelines. VL suppression was determined using the FDA snapshot algorithm; we pre-specified the main threshold as 400 copies/ml and non-inferiority margin of 12% for each randomised comparison.

**Results:** We enrolled 464 patients at 7 sub-Saharan African sites (61% female, 51% CD4<200, 28% VL≥ 100,000). At baseline, 58% overall had intermediate-high level resistance to tenofovir and 92% had resistance to lamivudine. Week 96 VL was <400 copies/ml in 89.8% in the dolutegravir group and 86.9% in the darunavir group (difference 2.9%; 95%CI, -3.0 to 8.7%; P=0.332; indicating non-inferiority of dolutegravir, without superiority); responses were equally good in the subgroups with no predicted-active NRTIs in the prescribed regimen. To date (>80% sequencing completed), 6 patients have intermediate-high level dolutegravir resistance (2 occurring after week 48) and 0 have darunavir resistance. In the other randomized comparison, VL was <400 copies/ml in 91.8% in the tenofovir group and 84.8% in the zidovudine group (difference 7.0%; 95% CI, 1.2 to 12.8%; P=0.019 indicating superiority of tenofovir); VL rebound ≥1000 copies/ml occurred in 5.6% in the tenofovir group and 14.3% in the zidovudine group (difference -8.7%, 95% CI -14.1 to -3.3%; P=0.002). Of 6 cases of dolutegravir resistance, 5 occurred in the zidovudine group. Grade 3/4 adverse events were similar in frequency between groups.

**Conclusion:** Dolutegravir and darunavir-based regimens maintain high levels of viral suppression at 96 weeks in second-line therapy, even when used with NRTIs that have no predicted activity. Dolutegravir resistance does not increase substantially during later follow-up. Tenofovir is superior to zidovudine and may protect against dolutegravir resistance. Guidelines that recommend switch from tenofovir to zidovudine for second-line therapy in the public health approach should be reconsidered.

NADIA Efficacy outcomes at week 96

| Outcome | Dolutegravir Group (N=235) | Darunavir Group (N=229) | Difference (95% CI) *Percentage points* | P | Tenofovir Group (N= 233) | Zidovudine Group (N= 231) | Difference (95% CI) *Percentage points* | P |
|---|---|---|---|---|---|---|---|---|
| **HIV-1 RNA level, intention-to-treat population - no (%)** | | | | | | | | |
| < 400 copies/ml | 211 (89.8) | 199 (86.9) | 2.9 (-3.0 to 8.7) | 0.332 | 214 (91.8) | 196 (84.8) | 7.0 (1.2 to 12.8) | 0.019 |
| ≥ 400 copies/ml | 20 (8.5) | 25 (10.9) | - | - | 13 (5.6) | 32 (13.9) | - | - |
| No virological data<br>Withdrew because of AE/death<br>Withdrew for other reasons | 4 (1.7)<br>3 (1.3)<br>1 (0.4) | 5 (2.2)<br>5 (2.2)<br>0 | - | - | 6 (2.6)<br>6 (2.6)<br>0 | 3 (1.3)<br>2 (0.9)<br>1 (0.4) | - | - |
| **HIV-1 RNA level (sensitivity analyses) – no (%)** | | | | | | | | |
| < 400 copies/ml (adjusted) | 90.2 | 86.7 | 3.5 (-2.8 to 9.8) | 0.278 | 92.4 | 84.5 | 7.9 (1.9 to 14.0) | 0.010 |
| VL < 400 copies (per protocol) | 203/218 (92.2) | 192/211 (91.0) | 1.2 (-4.0 to 6.5) | 0.652 | 206/216 (95.4) | 187/213 (87.8) | 7.6 (2.4 to 12.8) | 0.005 |
| **Secondary and other efficacy outcomes** | | | | | | | | |
| VL < 1000 c/ml- no (%) | 213 (90.6) | 203 (88.6) | 2.0 (-3.6 to 7.5) | 0.481 | 216 (92.7) | 200 (86.6) | 6.1 (0.6 to 11.6) | 0.030 |
| VL< 50 c/ml – no (%) | 189 (80.4) | 172 (75.1) | 5.3 (-2.2 to 12.9) | 0.168 | 188 (80.7) | 173 (74.9) | 5.8 (-1.8 to 13.3) | 0.133 |
| Confirmed VL rebound ≥ 1000 copies/ml – no (%) | 20 (8.5) | 26 (11.3) | -2.8 (-8.3 to 2.6) | 0.306 | 13 (5.6) | 33 (14.3) | -8.7 (-14.1 to -3.3) | 0.002 |

## 138 LENACAPAVIR AS PART OF A COMBINATION REGIMEN IN TREATMENT NAÏVE PWH: WEEK 54 RESULTS

**Samir Gupta**[1], James Sims[2], Cynthia Brinson[3], Frederick A. Cruickshank[4], Godson Oguchi[5], Javier Morales[6], Theo Hodge[7], Craig Dietz[8], Angela S. Liu[9], Laurie VanderVeen[9], Hadas Dvory-Sobol[9], Martin Rhee[9], Jared Baeten[9], Ellen Koenig[10]

*[1]Indiana University, Indianapolis, IN, USA, [2]St. Hope Foundation, Bellaire, TX, USA, [3]Central Texas Clinical Research, Austin, TX, USA, [4]Rosedale Infectious Diseases, Huntersville, NC, USA, [5]Midland Florida Clinical Research Center, LLC, Deland, FL, USA, [6]Clinical Research Puerto Rico Inc, San Juan, PR, USA, [7]Washington Health Institute, Washington, DC, USA, [8]Kansas City Care Health Center, Kansas City, MO, USA, [9]Gilead Sciences, Inc, Foster City, CA, USA, [10]Instituto Dominicano de Estudios Virológicos, Santo Domingo, Dominican Republic*

**Background:** Lenacapavir (LEN), a potent first-in-class inhibitor of capsid function, is in development for treatment and prevention of HIV-1. CALIBRATE is an ongoing, open-label, Phase II study evaluating subcutaneous (SC) and oral LEN, in combination with other antiretrovirals, in treatment-naïve people with HIV-1 (PWH). At Week 28 (W28), LEN + emtricitabine/tenofovir alafenamide (F/TAF) led to high rates of virologic suppression (94%).

**Methods:** Participants were randomized (2:2:2:1) to 1 of 4 treatment groups (TG). TG1 and TG2 both received SC LEN + oral daily (QD) F/TAF for 28 weeks, after which virologically-suppressed participants continued a 2-drug maintenance regimen: SC LEN with QD TAF (TG1) or QD bictegravir (B, BIC) (TG2). TG3 received oral QD LEN + F/TAF and TG4 received oral QD B/F/TAF throughout. We report the primary endpoint at W54. The study did not have prespecified formal statistical comparisons between TGs.

**Results:** 182 participants (7% female, 52% Black) were randomized and dosed (n=52, 53, 52, 25 in TG1 to TG4). Median age was 29 years; 15% had VL>100,000 c/mL. At W28 (as previously reported), 94%, 92%, 94%, and 100% had VL <50 c/mL by FDA Snapshot algorithm. At W54, 90%, 85%, 85%, and 92% had VL<50 c/mL; in TG1 to TG3 (i.e. those who received LEN), the majority of the remaining participants had discontinued study drug or achieved VL <50 c/mL later. Among those with VL <50 c/mL at W28 when starting the 2-drug maintenance regimen in TG1 and TG2, 94% and 92% had VL <50 c/mL at W54. For participants in TG1 to TG3, CD4 count increased by a median of 219 cells/μL (Q1, Q3: 102, 318) at W54 (vs 177 [30, 290] in TG4). No participant experienced a study drug-related serious adverse event (SAE). Three participants in TG2 discontinued LEN due to AEs of injection site reactions (ISRs) (Grade 1 induration, n=2; Grade 1 erythema/swelling, n=1). In TG1 and TG2 (i.e. those who received SC LEN), LEN-related ISRs included erythema (27%), swelling (23%), and pain (19%), which were mostly mild or moderate. In TG1 to TG3, the most frequent non-ISR AEs were headache and nausea (13% each).

**Conclusion:** LEN, given subcutaneously or orally in combination with TAF, BIC, or F/TAF, maintained high rates of virologic suppression at one year and was well-tolerated. These results support ongoing evaluation of LEN, as both injectable and oral formulations, in combination with other antiretroviral agents for the treatment of HIV-1 infection in individuals with diverse needs.

## 139 VIRAL ESCAPE DURING TRIPLE BROADLY NEUTRALIZING ANTIBODY THERAPY AGAINST HIV-1

**Boris Juelg**[1], Kathryn E. Stephenson[2], Kshitij Wagh[3], Victoria E. Walker-Sperling[2], Tom Hassell[4], Allen DeCamp[5], Elena E. Giorgi[3], Richard A. Koup[6], John R. Mascola[7], Roberto C. Arduino[8], Edwin DeJesus[9], Nicole L. Yates[10], Michael Seaman[2], Bette Korber[3], Dan Barouch[2]
*[1]Massachusetts General Hospital, Boston, MA, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]Los Alamos National Laboratory, Los Alamos, NM, USA, [4]International AIDS Vaccine Initiative, New York, NY, USA, [5]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [6]National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, [7]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, [8]University of Texas at Houston, Houston, TX, USA, [9]Orlando Immunology Center, Orlando, FL, USA, [10]Duke University, Durham, NC, USA*

**Background:** HIV-1 therapy with single or dual broadly neutralizing antibodies (bNAbs) has shown viral escape, indicating that at least a triple bNAb therapy may be needed for robust suppression of viremia. Complementary viral coverage resulting in extended breadth and potency has been modeled for multiple bNAb combinations and the combination of the CD4bs antibody VRC07-523LS, the V3-glycan antibody PGT121 and the V2-apex antibody PGDM1400 has been identified to cover 99% of cross clade strains of which 82% would be covered with at least 2 active antibodies (at $IC_{80}$ of <10ug/ml).

**Methods:** To determine whether the triple combination of PGDM1400, PGT121 and VRC07-523LS is safe and active against HIV in humans, we initiated a two-step Phase I study: Part 1 was a single-center, randomized, double-blind, dose-escalation, placebo-controlled trial to evaluate three intravenous doses of PGDM1400 alone or in combination with PGT121 (3, 10, and 30 mg/kg per antibody, respectively) in adults without HIV. Part 2 was a multi-center, open-label trial of a single intravenous (IV) administration of 20 mg/kg of PGDM1400, PGT121 and VRC07-523LS each or a single infusion of 30 mg/kg of PGDM1400+PGT121 each, in viremic adults with HIV not on ART. Clinicaltrials.gov #: NCT03205917

**Results:** PGDM1400 was safe and well tolerated at doses up to 30 mg/kg and when given in combination with PGT121 and VRC07-523LS. A single infusion of 20 mg/kg of each of the three antibodies reduced plasma HIV RNA levels in viremic individuals by a mean of 2.04 $log_{10}$ copies/ml, however, viral rebound occurred within a median of 20 days post nadir. Viruses present before antibody administration were all susceptible to VRC07-523-LS and in many cases were susceptible to PGT121 and PGDM1400. Rebound viruses demonstrated partial to complete resistance to PGDM1400 and PGT121, while susceptibility to VRC07-523-LS was largely preserved. Viral rebound occurred despite mean VRC07-523LS serum concentrations of 93 µg/ml.

**Conclusion:** To our knowledge, this is the first report of a triple antibody combination in humans for the treatment of HIV. While PGDM1400 and the combination of all three bNAbs were safe and well tolerated, our data highlight the critical requirement of broad antiviral activity and high serum concentrations that bNAb combinations need to achieve in order to maintain control over the virus.

## 140 PHASE I STUDY OF LONG-ACTING 3BNC117 AND 10-1074 IN VIREMIC ADULTS LIVING WITH HIV

**Marina Caskey**[1], Katrina Millard[1], Martina Turroja[1], Christian Gaebler[1], Erin Logue[2], Caroline S. Jiang[1], Leah Todd[1], Jacqueline D. Reeves[3], Christos Petropoulos[3], Timothy Wilkin[4], Pablo Tebas[2], Michel Nussenzweig[1]
*[1]The Rockefeller University, New York, NY, USA, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]Monogram BioSciences, San Francisco, CA, USA, [4]Weill Cornell Medicine, New York, NY, USA*

**Background:** Several anti-HIV-1 broadly neutralizing antibodies (bNAbs) targeting different envelope epitopes are being evaluated as long-acting alternatives or adjuvants to antiretrovirals (ART) for prevention and therapy, or as part of remission strategies. The combination of 3BNC117 and 10-1074 induced significant reductions in viremia and maintained viral suppression during ART interruption in individuals harboring antibody-sensitive viruses. Here, we evaluated the antiviral activity of the long-acting (LS) versions of these bNAbs during viremia.

**Methods:** This open-label Phase I study enrolled adults with chronic HIV not on ART, with plasma HIV-1 RNA ranging from 2.7-5.0 $log_{10}$ cp/ml, to receive single 30 mg/kg infusions of 3BNC117-LS and 10-1074-LS. Study endpoints were safety, pharmacokinetics, and effects on viremia, and follow up was of 24 weeks. Antibody sensitivity of circulating viruses was determined post-hoc by the PhenoSense mAb Assay. This phenotypic assay can generate HIV-1 pseudovirions expressing populations of plasma HIV-1 envelope sequences which are tested for neutralization sensitivity to bNAbs.

**Results:** Six male participants were enrolled with median baseline plasma HIV-1 RNA of 4.7 $log_{10}$ cp/ml (range 3.0-5.4 $log_{10}$ cp/ml). Antibody infusions were generally well tolerated. All 6 participants experienced decline in plasma HIV-1 RNA, with a median maximum decline of 1.86 $log_{10}$ cp/ml (range = 1.1-2.49 and SD = 0.48 $log_{10}$ cp/ml) reached at a median of 1.5 weeks following infusions. The observed magnitude of the decrease in viremia was similar to that observed after infusions of the unmodified 3BNC117 and 10-1074 (p 0.81). The decreased viremia was transient in 4 participants with baseline resistance in plasma to either 3BNC117-LS or 10-1074-LS, which means they effectively received functional monotherapy. In contrast, the 2 participants with plasma viruses that were sensitive to both antibodies and baseline plasma HIV-1 RNA of 3 and 3.5 $log_{10}$ cp/ml achieved and maintained undetectable HIV-1 RNA levels for the 24 weeks of follow up and > 12 weeks in the second participant who remains on study.

**Conclusion:** In this pilot study, the long-acting (LS) 3BNC117 and 10-1074 combination preserved antiviral activity and the potential to maintain long-term viral suppression in participants with sensitive viruses. Baseline antibody sensitivity of plasma viruses determined by the PhenoSense mAb Assay correlated with viremia decline and long-term suppression.

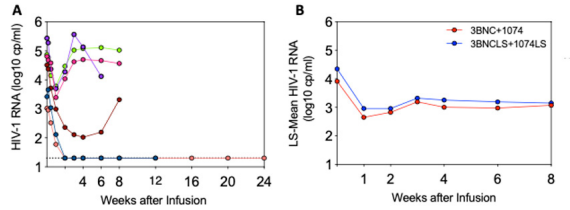



**Figure 1.** Plasma HIV-1 RNA levels following 3BNC117-LS/10-1074-LS or 3BNC117/10-1074 infusions in viremic adults with HIV. (**A**) HIV-1 RNA in $log_{10}$ copies per ml over 8 to 24 weeks following 3BNC117-LS/10-1074-LS combination (n=6), while participants remained off ART. (**B**) Average viral decline from day 0 through week 8 (least-squares means, by mixed effect linear model) after LS- (blue, n=6) or the unmodified bNAb combination (red, n=4). A linear mixed-effects was used to model the data and estimate whether there was a significant difference between the parental 3BNC117+10-1074 (Bar-On, Gruell et al. 2018) and the 3BNC117-LS+10-1074-LS combination therapy in viremic individuals, using time and treatment as fixed effects and a random intercept for each participant.

## 141 PREVALENCE OF SYPHILIS AND HIV/SYPHILIS COINFECTION IN 5 SUB-SAHARAN COUNTRIES

**Rose Killian**[1], Mansoor Farahani[2], Giles Reid[2], Godfrey Musuka[2], Samuel Biraro[2], Harriet Nuwagaba-Biribonwoha[2], Wafaa M. El-Sadr[2], Jessica E. Justman[2]
*[1]Columbia University, New York, NY, USA, [2]ICAP at Columbia University, New York, NY, USA*

**Background:** HIV and syphilis are common sexually transmitted infections globally and in sub-Saharan Africa (SSA); however, most prevalence data come from clinical cohorts. We examined the prevalence of syphilis in the general population and associated demographic and behavioral factors using Population-based HIV Impact Assessment (PHIA) surveys conducted by ministries of health of each country in collaboration with CDC and ICAP (2015-2017) in Tanzania, Uganda, Zambia, and Zimbabwe.

**Methods:** Consenting adults from randomly selected households provided demographic and behavioral information and blood samples for HIV and syphilis testing per each country's national guidelines. Chembio DPP® Syphilis Screen and Confirm Assay rapid diagnostic test was used to identify active syphilis, defined as positive for both Treponemal and non-Treponemal antibodies, with immediate return of results. We applied multivariable logistic regression models using survey weights (Table). Variances were estimated via the jackknife series.

**Results:** Among 104,093 adults (9,577 [9.2%] HIV+ and 94,516 [90.8%] HIV-), prevalence of active syphilis among HIV+ persons ranged from 2.9% (95% CI: 2.3%-3.6%) in Zimbabwe to 9.6% (95% CI: 8.1%-11.0%) in Zambia, while among HIV- persons, it ranged from 0.8% (95% CI: 0.7%-1.0%) in Tanzania to 2.1% (95% CI: 1.8%-2.4%) in Zimbabwe, which corresponds to an estimated 1,017,746

adults with active syphilis across 4 countries. HIV positivity was associated with increased risk for active syphilis, with an adjusted odds ratio (aOR) ranging from 2.5 (95% CI: 1.8-3.4) in Uganda to 5.9 (95% CI: 3.8-9.2) in Zimbabwe. Those divorced, separated, or widowed were more likely to have syphilis (aOR) ranging from 1.5 (95% CI: 1.1-2.0) in Uganda to 2.7 (95% CI: 1.7-4.3) in Zimbabwe. Those with multiple sexual partners in 12 months before surveys were more likely to have active syphilis, with aOR ranging from 1.6 (95% CI: 1.1-2.5) in Tanzania to 2.0 (95% CI: 1.2-3.3) in Zimbabwe. In Zimbabwe, condom use during the most recent sexual act was associated with lower odds of active syphilis (aOR 0.6: 95% CI: 0.4-1.0).

**Conclusion:** The high prevalence of active syphilis among HIV+ persons from the general population and a considerable number of infections among HIV- individuals in four SSA countries indicates the need for consistent and frequent screening for syphilis among PLHIV and at-risk groups and improved access to effective treatment for syphilis.

Table 1. Logistic Model Adjusted Odds Ratio (aOR) of Active Syphilis by Demographics and Risk Behaviors

| Predictor | | Tanzania | Uganda | Zambia | Zimbabwe |
|---|---|---|---|---|---|
| HIV status | Positive | 4.0*** | 2.5*** | 3.7*** | 5.9*** |
| | 95% CI | (2.7-5.8) | (1.8-3.5) | (2.9-4.7) | (3.8-9.1) |
| | Negative (ref) | - | - | - | - |
| Marital status | Divorced/Separated/Widowed | 1.3 | 1.5** | 1.7*** | 2.7*** |
| | 95% CI | (0.8-2.2) | (1.1-2.0) | (1.3-2.3) | (1.7-4.3) |
| | Married/Living together (ref) | - | - | - | - |
| Condom Use in the last sexual act | Yes | 1.4 | 1.4 | 0.8 | 0.6* |
| | 95% CI | (0.7-2.6) | (1.0-2.0) | (0.6-1.1) | (0.4-1.0) |
| | No (ref) | - | - | - | - |
| Number of Sexual partners in the past 12 months | 2+ | 1.6* | 1.1 | 1.7** | 2.0** |
| | 95% CI | (1.1-2.5) | (0.8-1.5) | (1.2-2.3) | (1.2-3.3) |
| | 1 (ref) | - | - | - | - |

*Note *: p-value<0.05 **: p-value<0.01 ***: p-value<0.001*
*The regression model also includes age, gender, and education, not shown here.*

## 142 CHANGES IN HIV AND STI TESTING AND DIAGNOSES DURING THE COVID-19 PANDEMIC

**Jennifer J. Chang**[1], Qiaoling Chen[1], Rulin C. Hechter[1], Jodie Dionne-Odom[2], Katia Bruxvoort[2]
*[1]Kaiser Permanente Southern California, Pasadena, CA, USA, [2]University of Alabama at Birmingham, Birmingham, AL, USA*

**Background:** The COVID-19 pandemic led to significant disruptions in the provision of routine medical services. Myriad pandemic-related factors such as access to healthcare facilities, virtual care delivery, social distancing, changes in sexual behaviors, and periodic swab shortages may have affected detection rates for HIV and other sexually transmitted infections (STIs). Thus, we evaluated trends in testing and diagnoses of chlamydia, gonorrhea, syphilis, and HIV from 2017 to 2020 in a large integrated health system in the United States.

**Methods:** We conducted a retrospective study using electronic health records among individuals ages ≥12 years enrolled in the Kaiser Permanente Southern California (KPSC) system. For each year from 2017 to 2020, we assessed the rates per 100,000 person-years of tests conducted and new positive results for genital and extragenital chlamydia, gonorrhea, syphilis, and HIV. Case definitions for chlamydia and gonorrhea included newly positive laboratory results in the absence of any other positive test within the past 30 days, or a positive test after a negative test within a 30-day period. Case definitions for syphilis included any new four-fold increase in RPR titer compared to the immediate prior RPR titer obtained within a 1-year period. We used Poisson regression to estimate rate ratios (RR) for each outcome, comparing pre-pandemic periods (January 2017 to February 2020) to the pandemic period (March to December 2020).

**Results:** The study included a population of more than 4 million KPSC members yearly. During the pre-pandemic period, rates of testing remained stable or modestly increased, whereas case rates increased for syphilis and chlamydia, and decreased for gonorrhea and HIV (Table 1). Compared to the pre-pandemic period, testing rates were significantly lower from March to December 2020 for all STIs and HIV (range of RR 0.69-0.83). HIV/STI diagnosis rates were 7-29% lower during the pandemic for HIV (RR 0.74 [0.66-0.83]), chlamydia (RR 0.71 [95% CI .70-0.73]), and gonorrhea (RR 0.93 [0.89-0.96]), but higher for syphilis (RR 1.32 [1.27, 1.37]).

**Conclusion:** We observed profound reductions in testing and diagnosis rates for chlamydia, gonorrhea, and HIV during the COVID-19 pandemic in Southern California compared to the pre-pandemic period. Despite lower pandemic period testing rates, syphilis diagnoses increased. These findings suggest the pandemic had an adverse impact on identification of STIs, which may impede efforts to curb STIs and the HIV epidemic.

Table 1. Incidence rates of STI testing and diagnoses

| Time Period | Unique patients | Total person-years | Chlamydia | | | | | | Gonorrhea | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Tests | Test rate* | Percent change in test rate** | Cases | Case rate* | Percent change in case rate** | Tests | Test rate* | Percent change in test rate** | Cases | Case rate* | Percent change in case rate** |
| 1 Jan 2017 - 31 Dec 2017 | 4193334 | 3682191 | 534177 | 14507 | | 18247 | 496 | | 534177 | 14507 | | 4439 | 121 | |
| 1 Jan 2018 - 31 Dec 2018 | 4337202 | 3809580 | 575767 | 15114 | 4 | 19843 | 521 | 5 | 575768 | 15114 | 4 | 4563 | 120 | -1 |
| 1 Jan 2019 - 29 Feb 2020 | 4609736 | 4520681 | 715087 | 15797 | 5 | 23815 | 526 | 1 | 715082 | 15797 | 5 | 5202 | 115 | -4 |
| 1 Mar 2020 - 31 Dec 2020 | 4327412 | 3318538 | 344776 | 10389 | -34 | 12167 | 367 | -30 | 344668 | 10386 | -34 | 3638 | 110 | -5 |
| Time Period | Unique patients | Total patient-years | Syphilis | | | | | | HIV | | | | | |
| | | | Tests | Test rate* | Percent change in test rate** | Cases | Case rate* | Percent change in case rate** | Tests | Test rate* | Percent change in test rate** | Cases | Case rate* | Percent change in case rate** |
| 1 Jan 2017 - 31 Dec 2017 | 4193334 | 3682191 | 324391 | 8810 | | 2327 | 63 | | 366329 | 9949 | | 538 | 15 | |
| 1 Jan 2018 - 31 Dec 2018 | 4337202 | 3809580 | 391512 | 9227 | 5 | 2690 | 70 | 10 | 392993 | 10316 | 4 | 532 | 14 | -4 |
| 1 Jan 2019 - 29 Feb 2020 | 4609736 | 4520681 | 468765 | 10356 | 12 | 3507 | 77 | 11 | 490785 | 10842 | 5 | 622 | 14 | -2 |
| 1 Mar 2020 - 31 Dec 2020 | 4327412 | 3318538 | 261231 | 7872 | -24 | 3056 | 92 | 19 | 257013 | 7745 | -29 | 347 | 10 | -24 |

* Per 100,000 person-years
** Change in case rate, from prior time period

## 143 CDC'S DIRECT-TO-CONSUMER DISTRIBUTION OF 100,000 HIV SELF-TESTS

**Epidemiology/Public** Health:

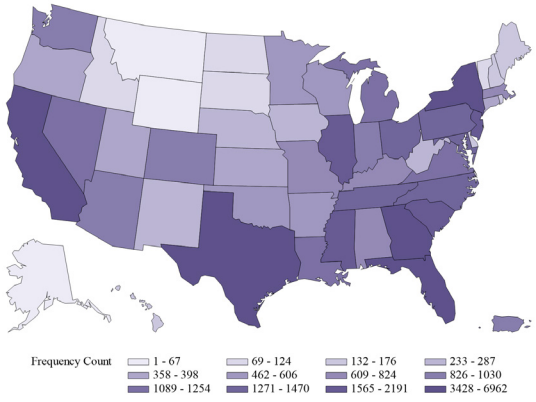
**Pollyanna R. Chavez**[1], Brian Emerson[1], Emily Lilo[1], Jennie Johnston Gayden[1], Euna August[1], Christopher Voegeli[1], Revae Downey[1], Emily Pingel[1], Kevin P. Delaney[1]
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** To directly support the federal Ending the HIV Epidemic (EHE) initiative and accelerate the identification of undiagnosed infections in the US, CDC implemented a program aimed to mail 100,000 HIV self-tests to prioritized populations at-risk for HIV through paid advertising, social media, and partner outreach.

**Methods:** CDC directed a marketing campaign to reach Black/African American and Hispanic/Latino gay men, transgender women, and Black/African American women living in areas of the US identified by the EHE initiative as having high HIV burden. Campaign messages included a weblink for a CDC-supported online ordering portal. Persons 17 years or older and living in the US or Puerto Rico could place an order for 1 or 2 HIV self-tests. Persons with HIV infection or taking pre-exposure prophylaxis (PrEP) were encouraged to share the test and not use it themselves. After placing an order, participants were invited to complete a short non-incentivized survey.

**Results:** The ordering portal was live for eight months (February 3, 2021-October 11, 2021). During this period, 56,458 persons placed an order. Three-fourths of participants (74.5%) ordered 2 HIV self-tests. Over half of the orders (55%) were placed from EHE locations, although orders were placed from all US states and Puerto Rico (Figure). The survey response rate was 82.2%. One-fourth of participants (26%) reported no prior HIV testing, while another 33% indicated that they were last tested for HIV more than a year ago. Some reported taking PrEP (4.9%) or testing positive for HIV prior to ordering (1.6%). Over a third of participants (36.7%) were non-Hispanic (NH) White persons, while 26.8% were Hispanic persons, and 24.8% were NH Black persons. Most participants (69.4%) identified as men, 26% as women, and 4.6% identified as another gender, including 1.4% transgender women. Most male participants (69%) reported having anal sex with a man in the past 12 months. Of the men who had sex with men, 17.0% were NH Black and 35% were Hispanic. Among women, 42.7% were NH Black, 29.7% NH White, and 19.3% were Hispanic.

**Conclusion:** CDC's first direct-to-consumer distribution of HIV self-tests resulted in 100,000 HIV self-tests being distributed in 8 months. This program highlights the demand for HIV self-tests, even reaching persons who never were tested for HIV. Clinicians, community-based organizations, and testing clinics should be aware that persons with preliminary positive HIV self-test results will require further testing and care.



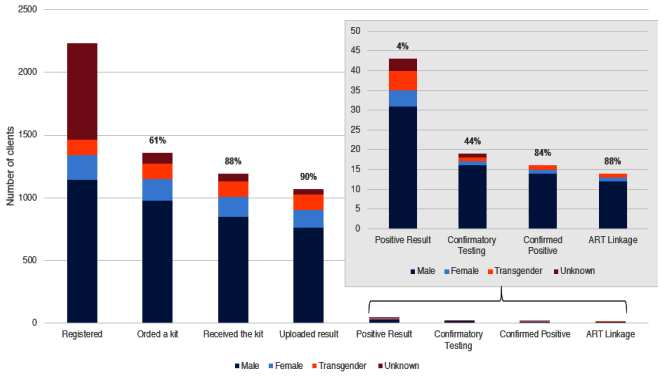
Oral Abstracts

## 144 HIV SELF-TESTING UNCOVERS HIGH BURDEN OF HIDDEN INFECTIONS IN INDIA

**Jalpa H. Thakker**[1], Aditya Singh[1], Rose Pollard[1], Jade Bell[1], Allison M. McFall[2], Mahender Taduri[3], Vikrant Gupta[3], Sangeeta Kaul[4], Jagadish T. Patil[3], Subash Ghosh[3], Ajay K. Enugu[1], Anthony Reddy[1], Shruti H. Mehta[2], Sunil S. Solomon[1]
*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]YR Gaitonde Center for AIDS Research and Education, Chennai, India, [4]United States Agency for International Development, New Delhi, India*

**Background:** The number of undiagnosed persons globally remains a barrier to achieving UNAIDS 95-95-95 goals. While nearly 80% are aware of their status, there is much variability by age and geography. Many of those undiagnosed are not engaging in traditional HIV services and do not visit physical locations; novel strategies are needed to overcome structural barriers. We implemented an online, HIV self-testing (HIVST) service for vulnerable populations in India.
**Methods:** An integrated web-based platform for HIVST www.safezindagi.net/selftesting was implemented across 24 Indian states in July 2021. Virtual outreach workers (vORWs) contacted clients on dating apps and social media platforms, provided counseling, and directed interested clients to HIVST via a platform that allowed for home delivery or pick up at a community site. HIVST could be assisted or unassisted with pre/post-test counseling from vORWS. Linkage to confirmatory testing/ART and PrEP was provided as needed. Descriptive statistics were used to characterize outcomes.
**Results:** Between June 30-October 21, 2021, 2,234 clients registered and 1,356 (61%) clients ordered an HIVST kit. Median age of the 1,356 clients was 27 years; 74% were male and 66% self-identified as MSM. Ten percent self-identified as transgender. In the prior 6 months, 67% reported condomless sex, 51% multiple partners, 13% transactional sex, 7% STIs, and 4% injection drug use. 1,190 clients (88%) received their kits within 3 days; 44% used a courier service and 56% picked up from a community site. Of 1,070 (90%) results uploaded, 43 (4%) were positive with geographical variability (5 states had >4% positivity). The median age of the positive clients was 30 years and 74% were male. Of importance, 65% reported condomless sex with multiple partners in prior 6 months and none were previously tested for HIV. 19 (44%) were linked to confirmatory testing of whom 16 (84%) were confirmed positive and 14 (88%) initiated ART at public centers (see Figure).
**Conclusion:** These data highlight the role of an HIVST platform to reach first time test-takers in a population with high risk behaviors and identified HIV burden >16 times the general population. With increasing online engagement and uptake of telemedicine globally, as well as continuing disruptions due to COVID-19, HIVST offers a critical approach to reach high-risk individuals, identify PLHIV, and link them to care and treatment.

HIV self-testing cascade among virtual platform clients across 24 Indian states by gender (June 30-Oct 21, 2021)

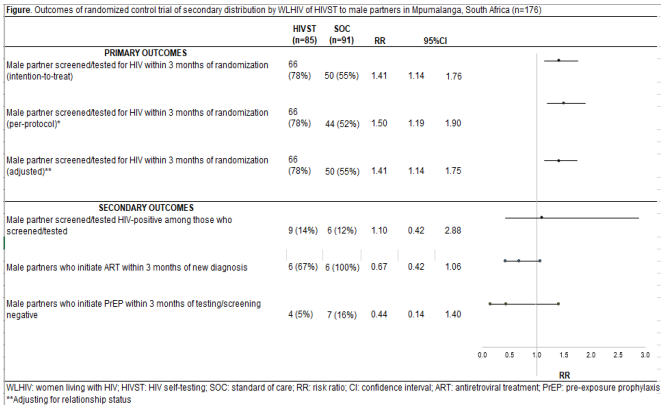



## 145 HIGH HIV SELF-TESTING OF MALE PARTNERS OF WOMEN LIVING WITH HIV IN RURAL SOUTH AFRICA

**Dvora Joseph Davey**[1], Kristin Wall[2], Nireshni Naidoo[3], Dhirisha Naidoo[3], Gugu Xaba[3], Claire Serrao[3], Silinganiso Chatikobo[3], Todd Malone[3], Kathryn Dovel[1]
*[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Emory University, Atlanta, GA, USA, [3]BroadReach Corporation, Cape Town, South Africa*

**Background:** South African men are underrepresented in HIV testing and treatment services. Secondary distribution of oral HIV self-test (HIVST) kits by women living with HIV (WLHIV) to their male partners may increase men's testing and treatment. Research in other countries demonstrates that secondary HIV self-testing (HIVST) distribution is acceptable and feasible among men and WLHIV who are in stable relationships, however, this may differ in South Africa where unmarried/non-cohabiting partnerships are common.
**Methods:** We evaluated the effectiveness of index partner HIV self-test (HIVST, Oraquick®) versus the standard of care (referral of male partners to return for facility-based HIV testing) on men's testing in a 1:1 randomized control trial. Eligibility criteria included WLHIV (18+ years) attending one of four high-density peri-urban and rural health facilities who self-reported having a primary male partner of unknown serostatus. The primary outcome was the proportion of WLHIV reporting that her partner tested for HIV within 3-months after enrollment. Secondary outcomes included positivity of men and linkage to ART within 3-months of diagnosis.
**Results:** Between March and July 2021, 176 WLHIV were randomized and followed to endline. Mean age of women was 35 years, 15% were pregnant and 38% were unmarried or in non-cohabiting relationships. At enrolment, most women were using ART (94%), were virally suppressed (88%). In the HIVST arm, 78% of men were reported to have used the HIVST (n=66 of 85) vs. 55% of men who tested in the clinic in the SOC (n=50 of 91) (RR=1.41; 95% CI=1.14, 1.76; Figure). In the HIVST arm, 9 men were reactive with HIVST (14% positivity), of which 6 were confirmed HIV-positive in the clinic (67%) and all of those started ART. Overall, 4 HIV-uninfected men started PrEP (5%). In the SOC, 6 men were diagnosed with HIV (12% positivity), 100% started ART, and 7 HIV-uninfected men started PrEP (16%). One case of verbal intimate partner violence was reported in the HIVST arm. In the HIVST group, 96% of WLHIV disclosed their HIV+ status to their partners (19% reported to disclose when her partner tested). Almost all (96%) said that testing was easy and accepted by their partners.
**Conclusion:** Secondary distribution of oral HIVST to partners by WLHIV was deemed acceptable and effective for linking male partners of WLHIV in rural South Africa to HIV diagnosis. Further interventions are needed to link reactive HIVST users to confirmatory HIV testing and ART services.

**Figure.** Outcomes of randomized control trial of secondary distribution by WLHIV of HIVST to male partners in Mpumalanga, South Africa (n=176)




WLHIV: women living with HIV; HIVST: HIV self-testing; SOC: standard of care; RR: risk ratio; CI: confidence interval; ART: antiretroviral treatment; PrEP: pre-exposure prophylaxis
**Adjusting for relationship status

## 146 SIX-MONTH PrEP WITH HIV SELF-TESTING TO IMPROVE DELIVERY KENYA: A RANDOMIZED TRIAL

**Kenneth Ngure**[1], Katrina Ortblad[2], Peter A. Mogere[3], Ashley Bardon[4], Dorothy Mangale[4], Catherine Kiptinness[3], Stephen Gakuo[3], Sarah Mbaire[3], Jacinta Nyokabi[3], Katherine K. Thomas[4], Nelly R. Mugo[3], Jared Baeten[4]
*[1]Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Kenya Medical Research Institute, Nairobi, Kenya, [4]University of Washington, Seattle, WA, USA*

**Background:** Oral pre-exposure prophylaxis (PrEP) is highly effective and being scaled at health clinics throughout sub-Saharan Africa. Barriers to clinic-based PrEP delivery such as high costs for clients and clinics remain. Innovative models that improve the efficiency of PrEP delivery without jeopardizing client outcomes are needed in this setting.
**Methods:** In a randomized non-inferiority implementation trial, we tested a novel model for PrEP delivery in Kenya: 6-month drug dispensing supported with interim HIV self-testing (HIVST). All participants were ≥18 years and had taken PrEP for 1 month. Participants were 2:1 randomized to: 1) 6-month PrEP dispensing (with semiannual clinic visits, supported by HIVST conducted at home after 3 months) or 2) standard-of-care (SOC) PrEP delivery (3-month supply with quarterly clinic visits). Our primary outcomes, measured at 6

months, were HIV testing, PrEP refilling, and PrEP adherence (detectable tenofovir-diphosphate in dried blood spots). We used binomial regression models to estimate risk differences (RDs) and interpreted 1-sided 95% confidence interval (CI) lower bounds (LB) ≥-10% as non-inferior.

**Results:** From May 2018 to February 2020, we enrolled and followed 495 participants: 165 men and 130 women in HIV serodifferent couples and 200 women not in known serodifferent couples. At 6 months, 83.3% (274/329) of those assigned the intervention tested for HIV compared to 84.3% (140/166) for SOC (RD -1.2%, 1-sided 95% CI LB -6.9%), Figure 1. Among intervention participants, 78.1% (257/329) refilled PrEP, compared to 80.7% (134/166) for SOC (RD -2.6%, 1-sided 95% CI LB -8.9%) and 60.8% (200/329) were adherent to PrEP compared to 57.2% (95/166) (RD 2.4%, 1-sided 95% CI LB -5.1%). In subgroup analyses among serodifferent couples, all women, and women singly-enrolled, findings were generally comparable to those among all participants. However, among women singly enrolled, PrEP adherence was 19.8% higher (2-sided 95% CI 5.8-33.8%) for those assigned the intervention compared to SOC, a superior result that was statistically significant. No participants acquired HIV.

**Conclusion:** Dispensing 6 months of PrEP with HIVST for interim testing at 3 months reduces the number of PrEP clinic visits in half without compromising HIV testing, PrEP refilling, or PrEP adherence. HIVST to support PrEP continuation can enable models of care that that require less frequent contact with the health system.

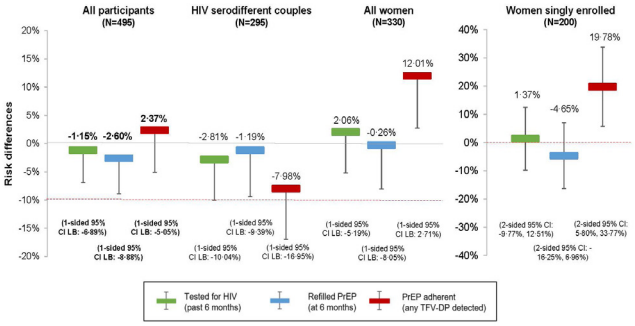



**Figure 1. The effect of six-month PrEP dispensing + interim HIVST on recent HIV testing, PrEP refilling, and PrEP adherence at six months**

These risk differences (RDs) compare the combined six-month PrEP dispensing + interim HIVST (either oral-fluid or blood-based) arm with the SOC PrEP dispensing arm at six months.

The primary pre-specified outcomes were recent HIV testing (green bars), PrEP refilling (blue bars), and PrEP adherence (red bars) among all participants (N=495, indicated in bold). We additionally pre-specified analysis of these outcomes among the following sub-groups: individuals taking PrEP who were members of HIV serodifferent couples (N=295), all women (N=330, including those enrolled in couples and those singly enrolled), and women singly enrolled (N=200).

## 147 SUCCESS OF ASSISTED PARTNER NOTIFICATION AMONG PATIENTS WITH PRIOR HIV DIAGNOSES

**Gillian L. O'Bryan**[1], Harugumi Chirairo[2], Farai Munyayi[2], Alison L. Ensminger[1], Gena L. Barnabee[1], Edington Dzinotyiweyi[3], Leonard Mwandingi[3], Laimi Ashipala[3], Norbert Forster[2], Gabrielle L. O'Malley[1], Matthew R. Golden[1]

*[1]International Training and Education Center for Health (I-TECH), University of Washington, Seattle, WA, USA, [2]International Training and Education Center for Health (I-TECH), University of Washington, Windhoek, Namibia, [3]Ministry of Health and Social Services, Windhoek, Namibia*

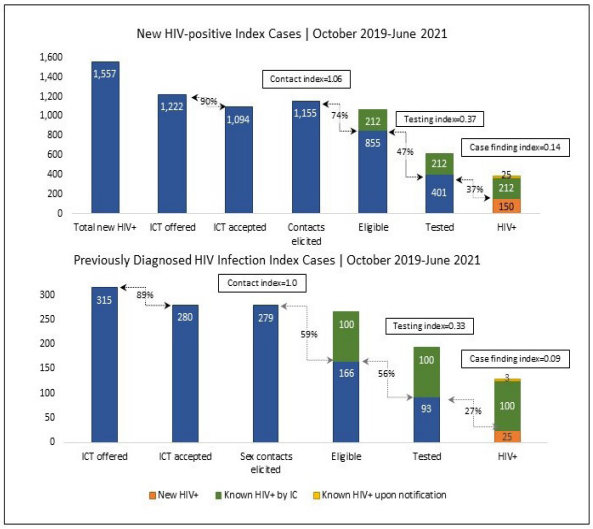
**Background:** Although many ministries of health recommend the provision of assisted partner notification services (APS) to selected patients with longstanding HIV diagnoses, few data exist on the effectiveness of APS in this population relative to persons with newly diagnosed HIV. We report APS outcomes among newly diagnosed and previously diagnosed index cases (ICs) in Namibia, a country estimated to be at 90-98-91 achievement of the UNAIDS 95-95-95 targets.

**Methods:** Staff in 22 Namibian Ministry of Health clinics offered APS to patients newly diagnosed with HIV infection and patients with previously diagnosed HIV who interrupted treatment or had viral loads >1,000 copies/mL. APS counselors used a structured interview guide to elicit information on ICs' sex contacts from the prior 24 months and assisted ICs arrange testing of contacts with unknown HIV status. We present program outcomes from October 2019 through June 2021 along the APS cascade for newly and previously diagnosed ICs, describing the contact index (contacts named per IC), testing index (contacts tested per IC), and case finding index (contacts tested positive per IC), and use generalized estimating equations to determine the association of case-finding with an IC being newly diagnosed (vs. a prior HIV diagnosis).

**Results:** Staff provided APS to 1,222 (78%) of 1,557 newly diagnosed ICs (Figure 1) identifying 1,155 sex contacts, 855 of whom were eligible for HIV testing. Of those, 401 tested and 150 (37%) were newly diagnosed with HIV. A total of 280 ICs with previously diagnosed HIV named 279 contacts; 93 contacts tested and 25 (27% of those tested) were newly diagnosed with HIV. Comparing new and previously diagnosed ICs, APS acceptance (90% vs. 89%), contact indices (1.06 vs. 1.00), and testing indices (0.37 vs.0.33) were similar. While the case-finding index was higher among newly diagnosed ICs than among previously diagnosed ICs (0.14 vs. 0.09), case finding was not significantly higher in the newly diagnosed ICs (p=0.45).

**Conclusion:** Although the case finding index was lower in ICs with previously diagnosed than in ICs with new HIV diagnoses, APS provided to patients who interrupted treatment or had viral loads >1,000 copies/mL successfully identified new HIV positive sex contacts in Namibia, a country where an estimated 90% of HIV positive people know their status. These findings support the provision of APS to selected patients with previously diagnosed HIV infection.

**Figure 1.** APS cascade for new HIV-positive index cases and index cases with previously diagnosed HIV infection (October 2019-June 2021)




## 148 LOW RISK OF ADVERSE EVENTS FOLLOWING ASSISTED PARTNER NOTIFICATION IN MOZAMBIQUE

**Matthew R. Golden**[1], Allend Mamudo[2], Ferruccio Vio[2], Erin Branigan[3], Zulmira Paredes[2], Adelina Maiela[2], Orvalho Augusto[1], Aleny Couto[4], Guita Amane[4], Noelia Chicuecue[4], Joaquim Wate[2]

*[1]University of Washington, Seattle, WA, USA, [2]International Training and Education Center for Health – Mozambique, Maputo, Mozambique, [3]International Training and Education Center for Health – Seattle, Seattle, WA, USA, [4]Ministry of Health, Maputo, Mozambique*

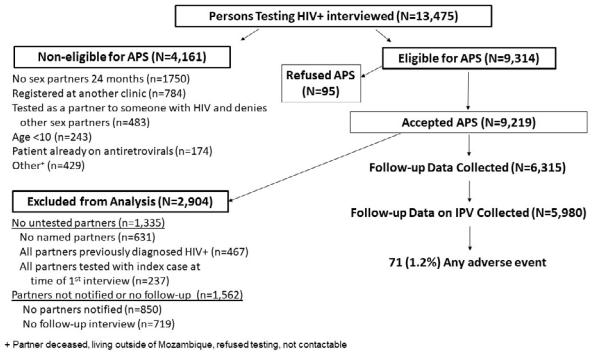
**Background:** The World Health Organization recommends that all persons diagnosed with HIV be offered assisted partner notification services (APS). There are limited data on the safety of APS as implemented in public health programs.

**Methods:** From January 2015 to March 2019, persons with newly diagnosed with HIV infection in 3 clinics in Maputo, Mozambique received APS using an APS model that relied on disclosure counseling and patient referral of sex partners, sometimes with a counselor's assistance (dual referral). APS staff routinely followed-up with APS recipients (index-cases [IC]) to determine if they had experienced adverse events following partner notification, including the following outcomes: 1) pushing, abandonment, or yelling; 2) being hit; or 3) loss of financial support or being expelled from the house.

**Results:** 18,965 persons tested HIV positive in the three clinics, 13,475 (71%) of whom were evaluated for APS eligibility, and 9,314 (69% of evaluated persons) were eligible to receive APS (Figure 1). Common reasons for ineligibility included reporting no sex partners in the prior 24 months (n=1,750, 42% ineligible), having already registered for HIV care at another clinic (n=784, 19% ineligible), and diagnosis as a partner of someone with HIV and reporting no other partners (n=483, 12% ineligible). Among eligible persons, 2,904 (31%) were excluded from analysis, either because they had no untested partners (n=1,335) or because they did not notify any partners (n=850) or had no follow-up interview

(n=719). Staff collected follow-up data from 5,980 ICs (95% of cases not excluded from analysis), among whom 71 reported an adverse event following partner notification. Adverse events occurred in 50 (1.3%) of 3,855 women and 21 (1%) of 2,125 men. Twenty-nine (0.5%) ICs reported experiencing violence after notifying a partner. 190 ICs reported a fear of adverse events at their initial APS interview, of whom 165 nevertheless elected to notify 205 partners, 96 (50%) of whom tested HIV positive. Four (2%) of 190 ICs who reported fear of adverse events experienced an adverse event following partner notification vs. 65 (1%) of 5,602 who had no such fear (p=0.238).

**Conclusion:** Adverse events following receipt of APS in Mozambique is uncommon. Although Mozambique's APS program did not promote partner notification among ICs who feared adverse events following partner notification, most ICs who had such a fear still elected to notify their partners and very few suffered adverse events.




### 149 LESSONS LEARNED FROM THE AMP TRIAL: IS THE GLASS HALF FULL?

**Carolyn Williamson**[1]
[1]*University of Cape Town, Cape Town, South Africa*

The AMP (Antibody Mediated Prevention) trial was the first study to show that a broadly neutralizing antibody (bnAb), VRC01, could prevent HIV-1 acquisition. However, this protection was incomplete, with VRC01 only blocking highly sensitive viruses. Here we will explore innate and selected resistance in breakthrough infections from this trial. Using an updated virus panel, we will place these results in the context of other clinically relevant bnAb interventions. In the AMP trial, VRC01 was found to prevent infection of viruses with IC80 against the VRC01 clinical product < 1 ug/ml, and it was estimated that a serum titre of 1:200 against circulating viruses was required for 90% prevention efficacy. To further examine the genetic barrier to resistance we used a novel PacBio deep sequencing approach to generate hundreds of viral envelope sequences per individual, at two timepoints. A subset of these sequences were cloned and evaluated for their neutralization sensitivity to a panel of bnAbs using a pseudovirus assay. In participants from HVTN703/HPTN081 AMP, which evaluated VRC01 to prevent infection in women from sub-saharan Africa, we demonstrated that the genetic bottleneck associated with transmission is more complex than previously estimated: we identified evidence of infection with low frequency variants; and in a subset of individuals infected with multiple viruses, we found that it was more common to harbour viruses that differed more than 2.5 fold in VRC01-neutralization sensitivity in the VRC01 arm compared to the placebo arm. This discordant VRC01 phenotype was due to both infection with viruses with a mixed phenotype, as well as evolution of resistance post-infection. While HIV-1 has diversified over the duration of the epidemic, this has had limited impact on sensitivity to bnAbs currently being evaluated in clinical trials. Thus, AMP informed the field in two important ways: firstly it showed that using bnAbs to prevent infection was possible and secondly it identified that VRC01 neutralization titre was a strong predictor of acquisition risk. We find evidence that VRC01 is not only exerting a selective pressure on the virus both prior to acquisition, but also post-acquisition. Although HIV-1 is diversifying as the epidemic progresses, there is limited antigenic drift supporting the use of combination bnAbs which can combat diversity and overcome the limitations of a single bnAb approach.

### 150 PUSHING THE ENVELOPE: mRNA VACCINES FOR COVID-19, HIV, AND OTHER PATHOGENS

**Drew Weissman**[1]
[1]*University of Pennsylvania, Philadelphia, PA, USA*

Vaccines prevent 4-5 million deaths a year making them the principal tool of medical intervention worldwide. Nucleoside-modified mRNA was developed over 15 years ago and has become the darling of the COVID-19 pandemic with the first 2 FDA approved vaccines based on it. These vaccines show greater than 90% efficacy and outstanding safety in clinical use. The mechanism for the outstanding immune response induction are the prolonged production of antigen leading to continuous loading of germinal centers and the adjuvant effect of the LNPs, which selectively stimulate T follicular helper cells that drive germinal center responses. Vaccine against many pathogens, including HIV, HCV, HSV2, CMV, universal influenza, coronavirus variants, pancoronavirus, nipah, norovirus, malaria, TB, and many others are currently in development. Nucleoside-modified mRNA is also being developed for therapeutic protein delivery. Finally, nucleoside-modified mRNA-LNPs are being developed and used for gene therapy. Cas9 knockout to treat transthyretin amyloidosis has shown success in phase 1 trials. We have developed the ability to target specific cells and organs, including lung, brain, heart, CD4+ cells, all T cells, and bone marrow stem cells, with LNPs allowing specific delivery of gene editing and insertion systems to treat diseases such as sickle cell anemia. Nucleoside-modified mRNA will have an enormous potential in the development of new medical therapies.

### 151 JUMP-STARTED IMMUNE RESPONSE: NOW, HOW TO TEACH BREADTH?

**William R. Schief**[1]
[1]*The Scripps Research Institute, La Jolla, CA, USA*

Please see the CROI 2022 Program Book for more information on this presentation.

### 152 CLINICAL EPIDEMIOLOGY OF AGING & COMORBIDITY WITH HIV INFECTION: A GLOBAL PERSPECTIVE

**Mark Siedner**[1]
[1]*Harvard Medical School, Boston, MA, USA*

Soon after the advent of combination antiretroviral therapy, it became evident that chronic, treated HIV infection was associated with an increased risk for non-AIDS co-morbidities. In the ensuing decades, data from the United States and Europe, and more recently from other global regions, have helped elucidate priority clinical syndromes that emerge more commonly in people living with HIV. In this talk, we will highlight some of the key data that has identified comorbidities and aging-related syndromes that are appear more common in PWH, describe the HIV-related epidemiologic risk factors that have been hypothesized to mediate risk of these conditions (eg nadir CD4 count, HIV viremia, co-infections, health behaviors), and highlight emerging data on distinct clinical phenotypes in the Global South, with a focus on sub-Saharan Africa. This talk will serve as an entree to other talks during this session on the mechanisms of risk, measuring comorbidity and aging in HIV clinical trials, and a discussion of priorities for to sustain health for people living with HIV as they age.

### 153 POTENTIAL BIOLOGIC MECHANISMS OF AGING IN HIV

**Nicholas Funderburg**[1]
[1]*The Ohio State University, Columbus, OH, USA*

People with HIV (PWH) are at an increased risk for several age related comorbidities, including cardiovascular disease and frailty. The underlying biological mechanisms that contribute to this increased risk are incompletely defined, but may include chronic inflammation, epigenetics, macromolecular damage, and/or changes in metabolism or the response to stress. By exploring the underlying biological mechanisms that may contribute to increased prevalence of age related comorbidities in PWH, appropriate intervention strategies may be identified.

### 154 INTEGRATING FRAILTY AND FUNCTIONAL OUTCOMES INTO CLINICAL TRIALS AND THE CLINIC

**Kristine Erlandson**[1]
[1]*University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

Maintaining a high level of physical function and avoidance of frailty are essential components of healthy aging. While there is a growing interest in assessing physical function and frailty among people aging with HIV, the implications are not always readily apparent. Among adults aging with HIV, frailty remains relatively uncommon, but impairments in physical function occur frequently, even among middle-aged people with HIV. In this presentation, frailty and physical function limitations will be defined and mechanisms

contributing to the increased burden will be reviewed. Considerations for incorporating frailty and physical function limitations in the setting of clinical studies will be discussed: for example, reversal of physical function limitations could be the primary outcome of an intervention, or frailty could be assessed to understand which populations best respond to an intervention. Lastly, the presentation will provide a framework for how physical function and frailty may be incorporated in the clinical setting for older adults with HIV.

**155 A COMPREHENSIVE APPROACH TO HIV PREVENTION IN PEOPLE WHO USE SUBSTANCES**

**Adam W. Carrico**[1]
[1]*University of Miami, Miami, FL, USA*

In the era of biomedical prevention, an established literature has focused on substance use and the pre-exposure prophylaxis (PrEP) care continuum in people who inject drugs (PWID) and sexual minority men (SMM) who use substances. First, I will provide an overview of the literature documenting key gaps in the PrEP care continuum. Second, I will highlight completed and ongoing randomized controlled trials that are testing the efficacy of interventions addressing the often-complex care needs of people who use substances to maximize the benefits of PrEP. Methods: A systematic review of the literature on the PrEP care continuum in PWID was identified that included 23 peer-reviewed publications. My team conducted a systematic review of the literature on the PrEP care continuum in SMM who use substances, which included 18 peer-reviewed publications focusing on adherence and persistence. Results: Despite high awareness and willingness to use PrEP among PWID, PrEP uptake has been low (0-3%). Low rates of uptake likely stem from multi-level barriers including individual-level (e.g., severity of substance use disorder symptoms), provider-level (e.g., stigma of substance-using patients), healthcare-related (e.g., poor infrastructure for PrEP delivery to PWID), and structural (e.g., homelessness, incarceration) determinants. Among SMM, those who use substances are as likely or more likely to use PrEP. Although SMM who use stimulants like methamphetamine experience more difficulties with daily oral PrEP adherence and persistence, they may achieve better PrEP adherence in the context of recent condomless anal sex (e.g., sexual event-driven dosing). At least two trials with PWID are focused on testing models of integrated care delivery (e.g., medications for opioid use disorder and HCV treatment) via mobile units, in opioid substitution therapy, or at syringe service programs. In addition, trials are testing contingency management (CM) for PrEP adherence in SMM who inject drugs and using CM as a platform for delivering a trauma-informed intervention for women who inject drugs. Similarly, other trials being conducted with SMM who use substances are focused on testing CM and motivational interviewing for supporting PrEP use, adherence, and persistence. Conclusions: Scalable, evidence-based interventions are needed to optimize PrEP uptake in PWID as well as PrEP adherence and persistence in SMM who use stimulants.

**156 TAILORING HIV PREVENTION STRATEGIES FOR THE UNIQUE NEEDS OF TRANSGENDER AND NONBINARY**

**Sari Reisner**[1]
[1]*Brigham and Women's Hospital, Boston, MA, USA*

This presentation will discuss the most current data on novel approaches to HIV prevention among transgender and nonbinary persons.

**157 HIV PREVENTION APPROACHES TAILORED TO INDIVIDUALS ENGAGED IN SEX WORK**

**Frances M. Cowan**[1]
[1]*Liverpool School of Tropical Medicine, Liverpool, UK*

Globally individuals who sell sex are disproportionately affected by HIV. They comprise a diverse group facing myriad challenges which vary by both individual level factors including age, gender identify, duration of selling sex and sex work typology as well as community/environmental factors such as background HIV prevalence and the pervading legal, cultural and social environments. Both individual and community level factors likely change over an individual's 'sex work life course' with individuals transitioning into and out of sex work and moving between geographic locations. Ensuring continued access to effective HIV-related prevention and care as part of comprehensive services over their sex work life course (including condoms, contraception, STI treatment, violence prevention and care, mental health support, harm reduction approaches to mitigate substance use, income generation opportunities and legal advice) is essential to reduce their vulnerability. There is good evidence that comprehensive approaches that reduce sex worker vulnerability and build their empowerment more generally foster engagement across all stages of the HIV prevention and care cascades and in addition have the potential to improve their overall health and human rights. Pre-Exposure Prophylaxis allows HIV negative sex workers to minimise their risk of HIV acquisition but many individual and community level barriers to its uptake, adherence and continued use exist. While uptake of PrEP among sex workers globally is starting to increase, in many settings adherence to PrEP and its continued use has been problematic and is often poorly understood, undermining both its individual and population level impact. Newer technologies (long acting injectables etc) can be highly effective and overcome many of the barriers associated with daily pill taking, but by themselves have little impact on the structural and behavioral barriers to uptake and continuation. Risk differentiated interventions to support optimal use of PrEP in all its forms and in combination with other HIV prevention, tailored to individual circumstances need to be co-developed / locally adapted in partnership with the sex work community to ensure they are effectively integrated into existing community programs and reflect the specific needs of sex workers in those communities. Evidence for effective approaches will be reviewed.

# POSTER ABSTRACTS

**158 WITHDRAWN**

**159 INFECTION OF FORESKIN MYELOID CELLS BY SUBTYPE C TRANSMITTED FOUNDER HIV-1 STRAINS**

New Investigator Scholar

**Bokani Nleya**[1], Ebrahim Steenkamp[1], Lester Sigauke[1], Sonwabile Dzanibe[1], Clive Gray[1], Frank Kirchhoff[2], David G. Russell[3], Nyaradzo T. Tsikiwa-Chigorimbo[1]
*[1]University of Cape Town, Cape Town, South Africa, [2]Ulm University Medical Center, Ulm, Germany, [3]Cornell University, Ithaca, NY, USA*

**Background:** The human foreskin is an efficient mucosal effector site enriched for innate and adaptive immune cells. The inner and outer foreskin have been shown to harbour CD4+CCR5+ cells co-expressing various C-type lectin receptors reported to augment HIV infection. Langerhans cells (LCs), macrophages and other dendritic cell subsets that may be permissive to HIV infection, have been detected in the foreskin. To investigate the susceptibility of these cells to HIV infection, we set up a pluricellular model and exposed them to HIV in-vitro.

**Methods:** Foreskin specimen obtained from 15 adult South African men undergoing voluntary medical male circumcision, were used to set up a pluricellular infection model. Briefly, subtype C transmitted founder (T/F) infectious molecular clones (IMCs) and prototypic controls were transfected in HEK293T cells to produce infectious virions. The TZM-bl assay was used to determine infectious titres that were used to infer MOIs. Migratory foreskin cells were infected at normalized MOIs and maraviroc was used to inhibit HIV infection. HIV infected cells were identified by p24 expression and further characterized by a multiparameter flow panel: CD207, CD1a, CD80/86, HLA-DR, CD11c, CD209, CD206, CD14, CD4, CCR5, CD3, CD45, CD169.

**Results:** Intracellularly stained foreskin granulocytes were shown to permit ex vivo HIV infection, average p24 expression from the concatenated live granulocytes was 6.67%, which showed an incremental trend in MFIs with time (p=0.0649). Of these, 3.49 % were either CD11c+CD14-, CD11c-CD14+ or CD11c+CD14+, and predominantly CD4+CCR5+ (79.2%). CD1a+CD207+ LCs constituted 0.87% of the p24+ population, with 83% CD4+CCR5+ expression. LCs, DC-like and macrophage-like cells all supported R5 NL4-3 and Bal-Env-NL4-3 replication significantly more efficiently than that of Subtype C ZM246-10 T/F (p=0.001) and X4 NL4-3 (p=0.0001). Maraviroc significantly blocked HIV infection by 82% (p=0.0175). Differential susceptibility was also observed among different participants.

**Conclusion:** The foreskin epidermis harbours heterogenous populations of CD4+CCR5+ myeloid cells that differentially support R5 HIV replication.

**160 MIGRATORY T CELLS ARE MORE SUSCEPTIBLE TO HIV-1 INFECTION VIA INCREASED VIRAL ENTRY**

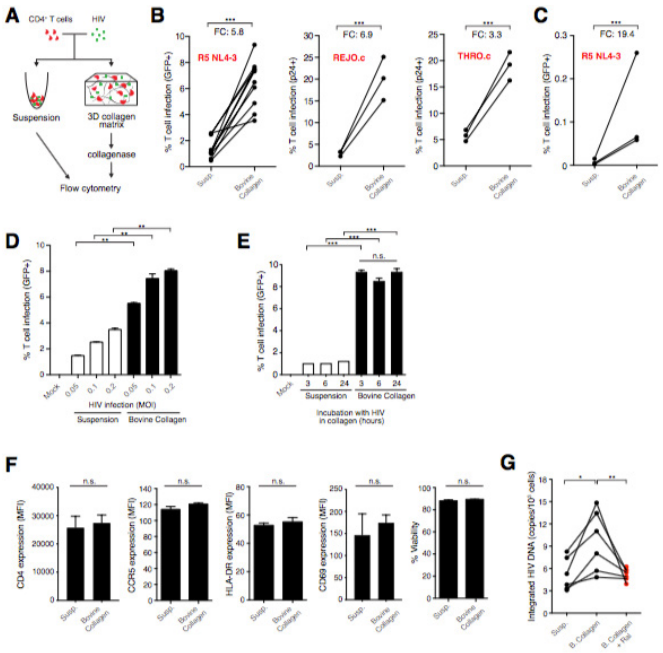
**Paul G. Lopez**[1], Oluwaseun E. Ajibola[1], Amélie Pagliuzza[2], Romaniya Zayats[1], Wan Hon Koh[3], Alon Herschhorn[4], Nicolas Chomont[2], Thomas T. Murooka[1]
*[1]University of Manitoba, Winnipeg, Canada, [2]Centre de Recherche du CHUM, Montreal, Canada, [3]University of Toronto, Toronto, Canada, [4]University of Minnesota, Minneapolis, MN, USA*

**Background:** The highly organized secondary lymphoid organs are the primary site of HIV replication, transmission and CD4+ T cell depletion. This environment allows T cells to actively migrate along reticular networks in search for cognate antigen, but how these behaviors impact HIV entry and productive infection remains unclear. Previous in vitro studies often investigate HIV infection using 2D culture systems, which do not take into account the migratory behaviors of T cells in vivo.

**Methods:** In this study, we compared the difference in behaviors, F-actin fluctuations and HIV infection of CD4+ T cells using collagen matrices that either support or restrict cell migration. The changes in cellular behaviors and phenotypes under various collagen chambers were assessed using two-photon 3D live imaging. Viral infection and cell subset analysis were performed using flow cytometry. The impact of ARV drugs and small molecule inhibitors were also explored. To measure how migration modulates viral entry and integration, HIV fusion (Vpr-Blam) assay was used.

**Results:** We developed a novel approach to achieve high T cell infection using collagen gels without the need for long centrifugation, cationic polymers or peptide fragments. Active migration along the collagen fibers in 3D collagen matrix results in a consistent and significant enhancement in T cell infection by cell-free R5-tropic lab adapted (fold change (FC) increase of 5.8x) and transmitted/founder molecular HIV clones (REJO FC = 6.9x; THRO FC = 3.3x), compared to cells infected in suspension. Moreover, infection in collagen matrix results in higher HIV DNA integration (FC = 1.9x) that was not attributed to altered receptor/co-receptor expression, activation state or viability. We also observe high levels of HIV fusion (FC = 2.5x) and subsequent infection in migratory T cells, whereas non-motile T cell display low viral entry and integration.

**Conclusion:** Migratory T cells can access regions where HIV density is high, indicating that the act of migration leads to more encounters with cell-free viral particles during their routine migratory surveillance. This study demonstrates that the environmental context in which initial HIV:T cell encounters occur modulate HIV entry and DNA integration efficiencies, and further illustrates mechanisms by which HIV subverts T cell migratory behaviors to maximize viral dissemination to establish a chronic infection.




## 161 ACCUMULATION OF HIV-1 Env MUTATIONS LEADS TO HIGH-LEVEL RESISTANCE TO DOLUTEGRAVIR

New Investigator Scholar

**Yuta Hikichi**[1], Jennifer L. Groebner[1], Ann Wiegand[1], John W. Mellors[2], Mary F. Kearney[1], Eric O. Freed[1]

*[1]National Cancer Institute, Frederick, MD, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA*

**Background:** We recently reported that mutations in the HIV-1 envelope glycoprotein (Env) can broadly reduce viral susceptibility to ARVs by enhancing virus to spread in vitro via cell-cell transfer. We also identified multiple Env mutations in participants failing an integrase (IN) strand transfer inhibitor (InSTI)-containing regimen (ACTG study A5273) in the absence of resistance mutations in IN. The aim of the current study was to examine whether HIV-1 can develop high-level resistance to the InSTI dolutegravir (DTG).

**Methods:** In vitro selection experiments using the SupT1 T-cell line and several HIV-1 strains [subtype B NL4-3 and NL(AD8); and subtype C transmitted founder K3016] were performed over nearly one year with increasing concentrations of DTG (0.1 – 2,000 nM). Sequence analysis of IN/Env-coding regions was performed longitudinally. The env amplicons from virus replicating at 256 nM DTG were cloned into NL4-3 and the replication kinetics and cell-free infectivity were examined.

**Results:** Propagating HIV-1 NL4-3 in increasing DTG concentrations led to the sequential accumulation of Env mutations (Env-S162K, R298K, Q363R, and A541V). By contrast, no InSTI-resistance mutations in the IN-coding region were identified. The Env mutant containing the four substitutions (4X mutant) listed above exhibited faster-than-WT replication, but severely impaired cell-free infectivity, relative to WT. This suggests that the accumulated Env mutations strongly enhance the efficiency of cell-cell transfer. Replication of WT NL4-3 and Env-A541V was inhibited at 3 nM and 10 nM DTG, respectively. However, the 4X Env mutant could replicate at DTG concentrations up to 1 μM, indicating that accumulation of Env mutations can lead to high-level resistance to DTG in the context of spreading infection. Sequence analysis of clinically relevant HIV-1 isolates (both subtype B and C and using CXCR4 or CCR5 as coreceptors) also revealed accumulation of multiple Env mutations during long-term passaging in the presence of DTG, in the absence of InSTI-resistance mutations in the IN-coding region. These results indicate that the Env-dependent pathway to high-level DTG resistance is independent of virus subtype and co-receptor usage.

**Conclusion:** High-level DTG resistance in culture can arise via the accumulation of multiple Env mutations. These findings advance the understanding of how HIV-1 can evolve resistance antiretrovirals including the potent InSTI DTG in the absence of mutations in genes targeted by the drug.

## 162 N-GLYCOSYLATION SITE SIGNATURES OF HIV ENVELOPE IN POST-TREATMENT CONTROLLERS

New Investigator Scholar

**Elmira Esmaeilzadeh**[1], Behzad Etemad[1], Yijia Li1, Lavine L. Christy[2], James Regan[1], Colline Wong[1], Elizabeth Connick[3], Paul Volberding[4], Michael Seaman[2], Jonathan Li[1]

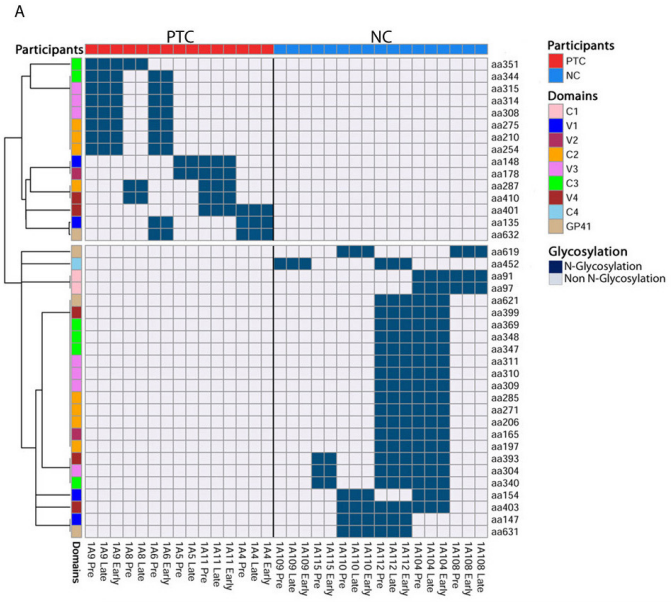
*[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]University of Arizona, Tucson, AZ, USA, [4]University of California San Francisco, San Francisco, CA, USA*

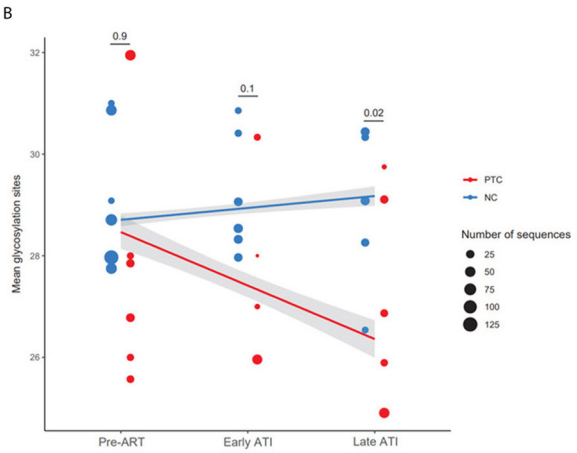
**Background:** HIV post-treatment controllers (PTCs) are individuals who can maintain viremia at low levels during treatment interruption. Viral evolution is frequently modulated by host immune pressures and comparing viral sequence changes in PTCs and post-treatment non-controllers (NCs) may provide insight on mechanisms behind HIV remission. N-glycosylation sites in HIV env play a critical role in viral evolution and immune escape against humoral immune responses. However, the link between the N-glycosylation and post-treatment control has not yet been established.

**Methods:** We performed single genome sequencing (SGS) PCR of env from plasma of 6 PTCs and 6 NCs for pre-ART, early (≤24 weeks), and late (>24 weeks) post-analytic treatment interruption (ATI) time points. To assess N-glycosylated sites dynamics at different time points, we used the GenSig tool of Los Alamos HIV sequence database. We used the R package "DESeq2" to evaluate differential N-glycosylation sites between PTCs and NCs groups in a comprehensive way. We used generalized estimating equation (GEE) to calculate between-group differences between PTCs and NCs at each time point. Benjamini-Hochberg P-value adjustment was used to account for multiple comparisons.

**Results:** The median early and late post-ATI viral loads in PTCs were 174 and 153 copies/ml, respectively and 4383 and 5662 copies/ml for the NCs. We observed a dynamic change in the pattern of N-glycosylated sites in HIV env between viruses over time in both PTCs and NCs. These changes were densely located in the gp120 domain of HIV env, specifically in V1 and V4 (median 32 for V1 and 26 for V4, P <0.01). PTCs and NCs demonstrated distinct sets of N-glycosylation sites (Figure 1A). In addition, we noted different trends in N-glycosylation site numbers between groups with N-glycosylation sites decreasing in PTCs (P<0.001) and remaining stable in NCs. Late post-ATI, NCs had significantly higher number of N-glycosylation sites in env than PTCs (P=0.02, Figure 1B).

**Conclusion:** We identified distinct patterns and dynamic changes in N-glycosylation sites between post-treatment controllers and non-controllers. These results suggest that distinct humoral immune responses may be present in the setting of HIV remission.






## 163 FUNCTIONALIZATION OF ENVELOPED PROTEIN NANOCAGES VIA DESIGNED TRANSMEMBRANE PROTEINS

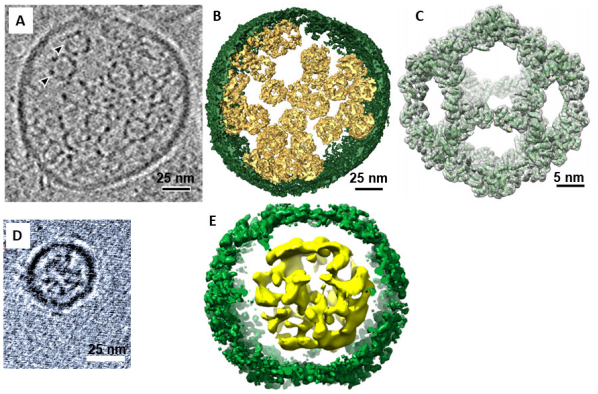
**Daniel Humphrys**[1], Wesley I. Sundquist[2], Neil King1, Ben Schmitz[2]
[1]*University of Washington, Seattle, WA, USA,* [2]*University of Utah, Salt Lake City, UT, USA*

**Background:** Extracellular vesicles (EVs) are an avenue for improved drug packaging and delivery, but engineering EVs remains challenging. To enable precise engineering of EVs, we developed Enveloped Protein Nanocages (EPN): EVs generated by designed proteins that induce their own release from cells inside cell-derived membrane envelopes. EPN are a genetically addressable platform that can be engineered to introduce new functions. Here we describe methods that functionalize EPN membranes via incorporation of designed and natural Transmembrane Proteins (TMP)

**Methods:** EPN Design: A SpyCatcher motif was added to self-assembling icosahedral scaffolding "cage" proteins (previously published); the cognate SpyTag was added to the intracellular side of the designed TMP. This resulted in an in-vivo covalently-bonded single peptide linking the cage to the TMP. Production: EPN were produced via transient transfection of cage and TMP plasmids into expi293F cells. Cells were pelleted 24-48hr post transfection, and the supernatant was filtered, then spun at 100,000g through a 20% sucrose cushion for 60min. The resulting pellet was resuspended in PBS for further work. Assays: Concentrated EPN was run on SDS-PAGE and assayed on Western blots to confirm the presence of the cage, TMP, and cage-TMP conjugate. EPN were incubated with trypsin to probe for correct TMP orientation and membrane integrity, contrasted against incubation of trypsin and triton resulting in disruption of the membrane and complete degradation. Imaging: EPN and EPN-TMP conjugates were imaged by cryo-electron microscopy, with reconstructed 3D densities.

**Results:** In contrast to the passive pseudotyping in EV-based technology, we used in-vivo covalent conjugation of TMP with EPN protein to create standardized, monodisperse, single-cage-per-EV Transmembrane Protein-Conjugated Enveloped Protein Nanocages (TMP-C-EPN). Protein Assays: Western blots showed the predicted protein sizes, including SDS-resistant covalently-conjugated TMP-cages species. This validated the designed TMP orientation, and that membrane integrity was maintained unless disrupted with detergent. EM imaging: Non-conjugated EPN average 100nm in diameter with 5-14 cages per EV. This contrasts with EM images of these TMP-C-EPN which show monodisperse, single-cages inside of a membrane approximately 30nm in diameter.

**Conclusion:** TMP-C-EPN are a promising new class of genetically encoded biomaterials, and generally highlight the utility of designed protein scaffolds that induce EV release.




CryoEM Reconstructions of EPN and TMP-C-EPN

**A)** CryoEM image of EPN from *Votteler et al. (2016)*
**B)** 3D density reconstruction of **A**
**C)** Cage structure from *Votteler et al. (2016)*
**D)** CryoEM image of TMP-C-EPN
**E)** 3D density reconstruction of **D**

## 164 MOLECULAR DETERMINANTS OF SARS-CoV-2 CELLULAR TROPISM IN VITRO

New Investigator Scholar

**Maritza N. Puray-Chavez**[1], Kyle M. LaPak[1], Shawn J. Mohammed[1], Dana Q. Lawson[1], Dennis Goldfarb[1], M. Ben Major[1], Sebla B. Kutluay[1]
[1]*Washington University in St Louis, St Louis, MO, USA*

**Background:** Lung cell lines to model SARS-CoV-2 replication in vitro are greatly limited hampering the rigorous study of SARS-CoV-2-host interactions. We analyzed a panel of 10 airway cell lines with various levels of ACE2 expression to identify models of SARS-CoV-2 infection. We found that none of the ACE2 expressing cell lines supported replication, whereas the H522 human lung adenocarcinoma cells were naturally permissive to SARS-CoV-2 infection despite detectable expression of ACE2. We confirmed that SARS-CoV-2 replication is indeed completely independent of ACE2 in H522s but dependent on heparan sulfates and the E484D substitution within the Spike. Further, we show that many of the ACE2 positive non-permissive cell lines express high basal levels of interferon-stimulated genes, which can be overcome by inhibition of the JAK/STAT pathway or by ACE2 overexpression. Together, our findings highlight ACE2-independent pathways can control the cellular tropism of SARS-CoV-2.

**Methods:** Conventional molecular virology assays have been conducted to study the permissiveness of a panel of 10 cell lines expressing various levels of ACE2. ACE2 independence of SARS-CoV-2 replication was validated by antibody blocking, Fc-ACE2 decoy peptide and CRISPR-based approaches in H522 cells. RNA sequencing was used to study the basal level of genes in the type-I IFN pathway in the panel of 10 cell lines, which was further validated by western blotting and qRT-PCR. A panel of 5 cell lines, with varying expression levels of ACE2 and TMPRSS2, were pre-treated with Ruxolitinib, a JAK inhibitor, and infected with SARS-CoV-2 strain 2019-nCoV/USA-WA1/2020 and spike variants. Viral replication was detected through analysis of cell associated RNA

**Results:** H522 human lung adenocarcinoma supports SARS-CoV-2 replication in a completely ACE2-independent manner. Transcriptomic analysis revealed basal high level of expression of interferon response pathway genes in some ACE2-positive cells recalcitrant to SARS-CoV-2 infection. Infection of OE21 and SCC25 cells required blocking of the IFN response pathway or ACE2 overexpression to allow SARS-CoV-2 infection.

**Conclusion:** These findings suggest that SARS-CoV-2 replication can proceed in complete absence of ACE2 and that the innate immunity is a key determinant of SARS-CoV-2 cellular tropism. These findings may explain the complex SARS-CoV-2 pathogenesis in vivo as it shows that factors independent of ACE2 can define cellular tropism.

**165 SPIKE MUTATION T403R ALLOWS BAT CORONAVIRUS RaTG13 TO USE HUMAN ACE2**

**Fabian Zech**[1], Daniel Schniertshauer[1], Christoph Jung[2], Alexandra Herrmann[3], Arne Cordsmeier[3], Janis Müller[4], Jana Krueger[1], Sandra Heller[1], Steffen Stenger[1], Alexander Kleger[1], Timo Jacob[2], Karl-Klaus Conzelmann[5], Armin Ensser[3], Konstantin Sparrer[1], Frank Kirchhoff[1]
*[1]Ulm University Medical Center, Ulm, Germany, [2]Ulm University, Ulm, Germany, [3]University Hospital Erlangen, Nuremberg, Germany, [4]Ulm University Medical Center, Nuremberg, Germany, [5]Ludwig Maximilians-Universität München, München, Germany*

**Background:** The bat coronavirus RaTG13 shares 96% sequence identity to SARS-CoV-2, the causative agent of the COVID-19 pandemic. However, the RaTG13 Spike (S) protein interacts only weakly with the human SCoV-2 receptor Angiotensin-converting Enzyme 2 (ACE2) and does not mediate efficient infection of human cells. Here, we examined which alterations are required to allow the RaTG13 S protein to use human ACE2 for efficient entry into human cells.
**Methods:** Sequence alignments showed that SARS-CoV-2 almost invariantly encodes a positively charged amino acid at position 403 of its S protein, while RaTG13 has a neutral Threonine (T). REAX based computational modeling suggested that S R403 contributes to binding of human ACE2. Wild-type and T403R mutant RaTG13 S proteins were investigated for their ability to bind ACE2 and to mediate infection of pseudotyped VSV particles in human lung- and intestine-derived cell lines as well as hPSC-derived gut organoids. Replication-competent recombinant SCoV2 S R403T was produced and replication monitored. In addition, we mutated human ACE2 to map the interacting residue of S R403. Finally, sera of vaccinated individuals were analyzed for their neutralizing potential against various WT CoV and RaTG13 S as well as mutant S containing pseudoparticles.
**Results:** Our results show that a single amino acid change of T403R allows the RaTG13 S to utilize human ACE2 for viral entry. Spike T403R enhanced infection of VSV-based RatG13 S pseudotypes in human lung and colon cells as well as gut-derived organoids. Vice versa R403T mutation reduced infectivity of SCoV2 S pseudotypes and recombinant SCoV2 replication. The enhancing effect of T403R in RaTG13 S depends on E37 in ACE2. RaTG13 T403R S-mediated infection was blocked by the fusion inhibitor EK-1 but not by the SCoV-2 antibody Casirivimab. SARS-CoV-2 and the T403R RaTG13 S were equally susceptible to neutralization by sera from individuals vaccinated against COVID-19.
**Conclusion:** A positively charged amino acid at position 403 in the S protein of bat coronaviruses is critical for efficient utilization of human ACE2. Our results help to better assess the zoonotic potential of bat sarbecoviruses and suggest that COVID-19 vaccination will also protect against closely bat relatives of SARS-CoV-2 that may emerge in the future.

**166 D614G AND OTHER MUTATIONS ARE CRITICAL FOR FITNESS OF NOVEL SPIKE VARIANTS**

**Leonid Yurkovetskiy**[1], Ann Dauphin[1], Matteo Bosso[1], Thomas Nyalile[1], Jeremy Luban[1]
*[1]University of Massachusetts, Worcester, MA, USA*

**Background:** During the beginning of the SARS-CoV-2 pandemic the D614G mutation in Spike protein appeared and became the first dominant variant across the globe. This mutation led to increased infectivity and stability of the spike protein and its importance is highlighted by being the one common mutation between every spike variant of concern that has come after the original. We asked how dependent spikes of subsequent lineages were on the D614G mutation and whether lineages in the absence of D614G had other mutations that increased fitness compared to the ancestral Wu-1 strain.
**Methods:** We explore the contribution of D614G and other identified stabilizing mutations on spike mediated infectivity by incorporating them into different spike constructs. Psuedotyped lentiviral and SARS-CoV-2 virus like particle (VLP) reporters are utilized along with biochemical analysis probing expression, processing, and incorporation of spike constructs into VLPs.
**Results:** We identify that the D614G mutation is critical for stability, infectivity, and virion loading in a number of prominent variants of concern and dominant lineages. Studying spike variants that were in circulation in absence of D614G mutation led to identification of a number of mutations at the S1 S2 interface performing similar stabilizing spike function as D614G, increasing infectivity compared to the ancestral Wu-1 Spike. The dependence on the presence of D614G or other stabilizing mutations only increased in the presence accumulating S1 mutations and specifically mutations that increase processing of spike by host furin protease, such as P681R.
**Conclusion:** Though D614G increased stability and infectivity on the Wu-1 background, other mutations are able to perform the same role. However as more mutations accumulated in spike in the presence of D614G other stabilizing mutations are unable to fully rescue infectivity in absence of D614G, indicating a clear reliance on D614G for function. Identifying this as a critical mutation in the spike may inform future vaccine design and prediction of possible mutations that are compatible with and functional on D614G containing spike lineages

**167 SARS-CoV-2 VARIANTS INCREASE KINETIC STABILITY OF OPEN SPIKE CONFORMATIONS**

**Ziwei Yang**[1], Yang Han[2], Shilei Ding[3], Wei Shi[4], Tongqing Zhou[4], Andrés Finzi[3], Peter D. Kwong[4], Walther Mothes[1], Maolin Lu[2]
*[1]Yale University, New Haven, CT, USA, [2]University of Texas Health Science Center at Tyler, Tyler, TX, USA, [3]Université de Montréal, Montreal, Canada, [4]National Institutes of Health, Bethesda, MD, USA*

**Background:** SARS-CoV-2 variants of concern harbor mutations in the Spike (S) glycoprotein that confer more efficient transmission and dampen the efficacy of COVID-19 vaccines and antibody therapies. S mediates virus entry and is the primary target for antibody responses, with structural studies of soluble S variants revealing an increased propensity towards conformations accessible to the human Angiotensin-Converting Enzyme 2 (hACE2) receptor. However, real-time observations of conformational dynamics that govern the structural equilibriums of the S variants have been lacking.
**Methods:** Here, we report single-molecule Förster Resonance Energy Transfer (smFRET) studies of S variants of concern containing critical mutations, including D614G and E484K, in the context of virus particles.
**Results:** Investigated variants were shown by smFRET to predominantly occupy more open hACE2-accessible conformations, agreeing with predictions from structures of soluble trimers. Additionally, S variants exhibited decelerated transitions from hACE2-accessible/bound states.
**Conclusion:** Here, we provide the real-time dimension to distinct structures of Spikes in the context of virus particles and present the first experimental evidence of increased stability of Spike variants. Our finding of increased S kinetic stability in the open conformation provides a new perspective on SARS-CoV-2 adaptation to the human population.

**168 MANNOSE-BINDING LECTIN (MBL) INHIBITS SARS-CoV-2 INFECTION AND REPLICATION IN VITRO**

**Isabel Pagani**[1], Matteo Stravalaci[2], Daniela Cesana[3], Pierangela Gallina[3], Nicoletta Pedemonte[4], Valeria Capurro[4], Nicola Clementi[1], Nicasio Mancini[1], Barbara Bottazzi[2], Alberto Mantovani[2], Elisa Vicenzi[3], Cecilia Garlanda[2]
*[1]San Raffaele Vita-Salute University, Milan, Italy, [2]Humanitas Clinical and Research Center, Milan, Italy, [3]San Raffaele Scientific Institute, Milan, Italy, [4]Giannina Gaslini Institute, Genova, Italy*

**Background:** Humoral innate immunity consists of a limited, but diverse, set of humoral fluid phase pattern recognition molecules (PRMs) that represent a first line of resistance against microbial invaders by promoting pathogen disposal by phagocytosis, complement activation and inflammation. These factors encompass complement, ficolin, collectin and pentraxin family of proteins.
**Methods:** We have analyzed the activity of PRMs for their potential capacity of inhibiting SARS-CoV-2 entry and replication into epithelial cells by a microneutralization assay based on a lentiviral particles pseudotyped with the SARS-CoV-2 spike protein in HEK293T cells overexpressing the angiotensin converting enzyme 2 (ACE2). Either SARS-CoV-2 or target cells were incubated with Mannose Binding Lectin (MBL, concentration range: 1-50 µg/ml) to further characterize its anti-viral activity for 1 h prior to infection in both human Calu-3 cells and air-liquid interface cultures of human bronchial epithelial cells (HBEC). Binding experiments were carried out with SARS-CoV-2 Spike protein and recombinant MBL to further investigate its antiviral action.
**Results:** Among 12 PRMs tested, only MBL inhibited viral entry in the pseudotyped neutralization assay. Furthermore, MBL protein inhibited SARS-CoV-2 viral replication in Calu-3 and HBEC by ca. one $\log_{10}$ at the top concentration (10 µg/ml and 50 µg/ml, respectively). MBL antiviral activity was confirmed also against alpha, beta and gamma SARS-CoV-2 variants of concern. Binding experiments showed that MBL specifically interacts with the trimeric form of SARS-CoV-2 spike.

**Conclusion:** MBL binds to the Spike protein in its active trimeric conformation leading to the inhibition of SARS-CoV-2 infection and replication in vitro. These results suggest that MBL possesses an antiviral activity against SARS-CoV-2 that could bear therapeutic potential.

## 169 SARS-CoV-2 SPIKE EXPRESSION AT THE SURFACE OF INFECTED HUMAN AIRWAY EPITHELIAL CELLS

**Shilei Ding**[1], Damien Adam[1], Guillaume Beaudoin-Bussières[1], Alexandra Tauzin[1], Shang Yu Gong[1], Romain Gasser[1], Annemarie Laumaea[1], Sai Priya Anand[1], Anik Privé[1], Catherine Bourassa[1], Halima Medjahed[1], Jérémie Prévost[1], Jonathan Richard[1], Emmanuelle Brochiero[1], Andrés Finzi[1]
*[1]Centre de Recherche du CHUM, Montreal, Canada*

**Background:** Emerging evidence points out to potential benefits from Fc-mediated effector functions in SARS-CoV-2 infection. Some Fc-mediated effector functions such as antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP) require recognition of the antigen at the surface of infected cells.
**Methods:** To evaluate the expression levels of SARS-CoV-2 Spike at the surface of infected airway epithelial cells, we developed an intracellular staining against SARS-CoV-2 nucleocapsid (N). This assay allows the distinction between infected versus uninfected cells. Human primary airway epithelial cells (pAECs) were infected with authentic SARS-CoV-2 D614G or Alpha variants. Infected cells were identified with an anti-N antibody and cell surface expression of Spike measured with the conformational-independent anti-S2 CV3-25 antibody.
**Results:** We found robust SARS-CoV-2 Spike expression at the cell surface of pAECs. Infected cells were readily recognized with plasma from convalescent and vaccinated individuals. Importantly, recognition of SARS-CoV-2 infected cells strongly correlated with Fc-mediated effector functions measured in a cohort of vaccinated naïve and previously-infected individuals.
**Conclusion:** Altogether, our findings further support the importance of measuring Fc-mediated effector function in infection and vaccination settings for SARS-CoV-2.

## 170 RESTRICTED INFECTION OF MACROPHAGES BY SARS-CoV-2 INDUCES PROINFLAMMATORY RESPONSES

New Investigator Scholar

**Sallieu Jalloh**[1], Judith Olejnik[1], Jacob Berrigan[1], Ellen L. Suder[1], Annuurun Nisa[2], Sanjay Tyagi[2], Yuri Bushkin[2], Elke Mühlberger[1], Suryaram Gummuluru[1]
*[1]Boston University, Boston, MA, USA, [2]Rutgers University, Newark, NJ, USA*

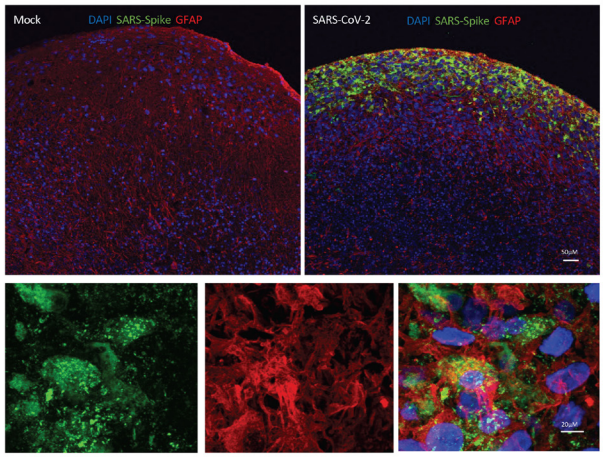
**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with immune hyperactivation and high levels of proinflammatory cytokines. Extensive lung infiltration by CD169+ inflammatory monocytes and presence of activated CD169+ alveolar macrophages suggest monocyte/macrophages are key drivers of severe morbidity and mortality. In this study, we determined whether CD169 mediated ACE2-independent SARS-CoV-2 entry and restricted viral genome replication in macrophages triggers pro-inflammatory cytokine expression.
**Methods:** Monocyte-derived macrophages (MDMs) and PMA-differentiated THP-1 macrophages engineered to constitutively express CD169, ACE2, or CD169 and ACE2 were infected with USA-WA1/2020/SARS-CoV-2 isolate with or without Remdesivir pre-treatment. To identify mechanism of innate immune activation, nucleic acid sensing pathways were selectively depleted in CD169+ macrophages. Extent of viral genomic (gRNA) and sub-genomic (sgRNA) expression and induction of pro-inflammatory cytokines was determined by qRT-PCR and single molecule RNA FISH analysis. Viral protein expression and infectious virus particle production was determined by immunofluorescence analysis and TCID50.
**Results:** While productive virus infection (viral protein expression and infectious virus particle release) was only observed in ACE2+ macrophages, SARS-CoV-2 N or S expression and infectious virus production was not observed in CD169+ macrophages. Co-expression of ACE2 and CD169 significantly enhanced infectious virus production and spread. Interestingly, smFISH and RT-qPCR analysis revealed CD169+ cells express cytosolic negative-strand gRNA and positive strand sgRNA. Importantly, CD169-mediated SARS-CoV-2 infection of macrophages and expression of viral mRNAs led to induction of pro-inflammatory cytokines, IL-6, TNFα, and IL-1β, despite lack of viral protein expression in CD169+ macrophages. Pre-treatment with Remdesivir blocked de novo expression of viral mRNAs and induction of inflammatory cytokines in CD169-dependent infection of macrophages. Furthermore, knockdown of cytosolic RLRs (RIG-I and MDA-5) or MAVS significantly attenuated inflammatory cytokine expression in CD169+ macrophages, confirming that nucleic acid sensing of restricted cytosolic viral mRNA expression in macrophages triggers innate immune activation.
**Conclusion:** These results suggest that restricted SARS-CoV-2 infection of CD169+ macrophages contributes to COVID-19-associated hyperinflammatory cytokine response.

## 171 NEUROPILIN-1 MEDIATES SARS-CoV-2 INFECTION OF ASTROCYTES PROMOTING NEURON DYSFUNCTION

New Investigator Scholar

**Weili Kong**[1], Mauricio Montano[1], Michael J. Corley[2], Ekram Wassim A. Helmy[1], Nadia Roan[1], Melanie M. Ott[1], Lishomwa Ndhlovu[2], Warner Greene[1]
*[1]Gladstone Institutes, San Francisco, CA, USA, [2]Weill Cornell Medicine, New York, NY, USA*

**Background:** SARS-CoV-2 primarily infects the lung but may also damage other organs including the brain, heart, kidney, and intestine. Central nervous system (CNS) disorders include loss of smell and taste, headache, delirium, acute psychosis, seizures, and stroke. Pathological loss of gray matter occurs in SARS-CoV-2 infection but it is unclear whether this is due to direct viral infection, indirect effects associated with systemic inflammation, or both.
**Methods:** We used iPSC-derived brain organoids and primary human astrocytes from cerebral cortex to study direct SARS-CoV-2 infection, as confirmed by Spike and Nucleocapsid immunostaining and RT-qPCR. siRNAs, blocking antibodies, and small molecule inhibitors were used to assess SARS-CoV-2 receptor candidates. Bulk RNA-seq, DNA methylation seq, and Nanostring GeoMx digital spatial profiling were utilized to identify virus-induced changes in host gene expression.
**Results:** Astrocytes were robustly infected by SARS-CoV-2 in brain organoids while neurons and neuroprogenitor cells supported only low-level infection. Based on siRNA knockdowns, Neuropilin-1, not ACE2, functioned as the primary receptor for SARS-CoV-2 in astrocytes. The endolysosomal two-pore channel protein, TPC, also facilitated infection likely through its regulatory effects on endocytosis. Other alternative receptors, including the AXL tyrosine kinase, CD147, and dipeptidyl protease 4 (DPP4), did not function as SARS-CoV-2 receptors in astrocytes. SARS-CoV-2 infection dynamically induced type I, II, and III interferons, and genes involved in Toll-like receptor signaling, MDA5 and RIG-I sensing of double-stranded RNA, and production of inflammatory cytokines. Genes activating apoptosis were also increased. Down-regulated genes included those involved in water, ion and lipid transport, synaptic transmission, and formation of cell junctions. Epigenetic analyses revealed transcriptional changes related to DNA methylation states, particularly decreased DNA methylation in interferon-related genes. Long-term viral infection of brain organoids resulted in progressive neuronal degeneration and death.
**Conclusion:** Our findings support a model where SARS-CoV-2 infection of astrocytes produces a panoply of changes in the expression of genes regulating innate immune signaling and inflammatory responses. Deregulation of these genes in astrocytes produces a microenvironment within the CNS that ultimately disrupts normal neuron function, promoting neuronal cell death and CNS deficits.




Four-month-old cerebral organoids were either mock-treated or infected with SARS-CoV-2 for 7 days. Immunostaining was performed; GFAP marks astrocytes depicted in red, and SARS-CoV-2 Spike is depicted in green. Scale bars are indicated.

## 172 GALECTIN-9 INDUCES SARS-CoV-2 REPLICATION AND INFLAMMATION IN AIRWAY EPITHELIAL CELLS

New Investigator Scholar

**Li Du**[1], Mohamed Bouzidi[1], Akshay Gala[1], Fred H. Deiter[2], Jean-Noël Billaud[3], Stephen T. Yeung[4], Prerna Dabral[1], Jing Jin[1], Graham Simmons[1], Zain Y. Dossani[1], Toshiro Niki[5], Lishomwa Ndhlovu[4], John Greenland[2], Satish Pillai[2]
*[1]Vitalant Research Institute, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]QIAGEN Digital Insights, Redwood City, CA, USA, [4]Weill Cornell Medicine, New York, NY, USA, [5]Kagawa University, Kagawa, Japan*

**Background:** Galectin-9 (Gal-9) is a β-galactoside-binding lectin involved in immune regulation and viral immunopathogenesis. Multiple recent reports demonstrate that plasma levels of Gal-9 are elevated in the setting of severe COVID-19 disease. However, a causal role of Gal-9 in SARS-CoV-2 pathology remains to be elucidated. Here, we determined the impact of Gal-9 on SARS-CoV-2 replication and pro-inflammatory signaling in immortalized and primary human airway epithelial cells (AECs).

**Methods:** Dose-dependent cytotoxicity of recombinant human Gal-9 in the Calu-3 AEC line was determined by MTT assay. Calu-3 cells were infected with SARS-CoV-2 isolate USA-WA1/2020 (MOI=0.01). Primary AECs were isolated from healthy donor lung transplant tissue, cultured at air liquid interface (ALI), and infected with SARS-CoV-2 lineage P.1 (MOI=0.1). SARS-CoV-2 replication was assessed by RT-PCR quantitation of the nucleocapsid (N) gene, immunofluorescence assay (IFA) of N protein, and titration of supernatant (TCID50). Viral entry was measured using luciferase activity of VSV-SARS-CoV-2 S-ΔG-Luciferase reporter pseudovirus. ACE2 and TMPRSS2 cell-surface expression were measured by flow cytometry. Pro-inflammatory factors (IL-6, IL-8, and TNFα) were detected by RT-PCR. Total RNA-seq was used to evaluate Gal-9 effects on the host transcriptome. Groups were compared by Student's t-test, and differential expression analyses were performed using DESeq2.

**Results:** Gal-9 reached 50% cytotoxicity in Calu-3 cells at 597 nM. Gal-9 significantly increased SARS-CoV-2 expression (8.1 to 25.5 fold; $p<0.0001$) and infectious virus release (1.9 to 17.8 fold; $p<0.038$) in a dose-dependent manner in Calu-3 cells. Pseudovirus entry into Calu-3 cells was enhanced by Gal-9 (2.4 to 5.6 fold; $p<0.0016$), and the enhanced entry was inhibited by anti-ACE2 antibody ($p<0.0027$). Cell surface ACE2 and TMPRSS2 expression were unaffected by Gal-9. Gal-9 treatment accelerated virus-induced expression of IL-6, IL-8, and TNFα ($p<0.018$) in Calu-3 cells. Gal-9 increased SARS-CoV-2 production ($p=0.03$) and pro-inflammatory factor expression ($p<0.05$) in primary AECs (N=5 donors). RNA-seq data revealed that Gal-9 significantly induced IL-17, EIF2, IL-8 and IL-6 signaling pathways in the setting of SARS-CoV-2 infection.

**Conclusion:** Gal-9 facilitates SARS-CoV-2 entry, replication, and virus-induced pro-inflammatory signaling in AECs ex vivo. Our data suggest that pharmacologic manipulation of Gal-9 should be explored as a SARS-CoV-2 therapeutic strategy.

## 173 THE EFFECTS OF TYPE I & II IFNs DISCLOSE A ROLE FOR DOPAMINE IN SARS-CoV-2 INFECTION

New Investigator Scholar

**Fiona Limanaqi**[1], Gioia Cappelletti[1], Micaela Garziano[1], Sergio Strizzi[1], Claudia Vanetti[1], Claudio Fenizia[1], Daria Trabattoni[1], Mario Clerici[1], Mara Biasin[1]
*[1]University of Milan, Milan, Italy*

**Background:** Recent studies highlight the dynamic nature of virus-host interaction during SARS-CoV-2 infection, raising intriguing questions about the role and timing of interferon (IFN) responses. In fact, SARS-CoV-2 delays/antagonizes Type-I, and to a definitely lesser extent, Type II-IFNs. While paving the way for potential antiviral therapies based on immune activation, the molecular mechanisms linking different IFN pathways to SARS-CoV-2 susceptibility remain to be elucidated. The present study investigates the role of Type-I & -II IFNs in SARS-CoV-2 replication in human lung cells, with a focus on molecular pathways related with innate and adaptive immunity.

**Methods:** Human lung carcinoma cells (CaLu3) were pretreated with IFN-α, -β or -γ (from 1 to 1000 U/mL), O.N. Cells were infected with SARS-CoV-2 (MOI 0.05) for 3h, and IFNs were added during infection. In another set of experiments, IFNs were added only p.i. Supernatants were harvested at 24 and 48h p.i. to assess viral replication by RT-qPCR, and to quantify the levels of cytokines/chemokines through Multiplex assay. At 48h post-infection, cells were collected and RNA was retrotranscribed to investigate a variety of transcriptional targets. Cell viability was assessed by MTT. Results are presented as the average of the relative expression units to the GAPDH gene, calculated by the $2^{-\Delta\Delta Ct}$ equation. Statistical analyses were performed through the Student t-test.

**Results:** Pretreatment with both Type-I & -II IFNs dramatically reduces SARS-CoV-2 replication in the absence of cell toxicity. Such an effect is maintained, though at a lower magnitude, when IFNs are added only p.i. The antireplicative effects of Type-I &-II IFNs are associated with both convergent and divergent mechanisms. Both Types decrease the expression and/or protein levels of most pro-inflammatory mediators while augmenting anti-inflammatory and anti-apoptotic factors. Surprisingly, IFN-γ shows the strongest effect in potentiating antiviral effectors besides boosting adaptive immunity pathways. Remarkably, a convergent effect of both IFN Types is observed upon the expression of genes associated with DA activity, including DA receptors (D1-D5) and the DA transporter (DAT), which are dramatically altered by SARS-CoV-2.

**Conclusion:** Both Type-I &-II IFNs halt SARS-CoV-2 replication by acting through complementary mechanisms. Their effects also disclose a potential role for DA activity, and neuromodulators in general, in host immunity during SARS-CoV-2 infection in pulmonary cells.

## 174 CHARACTERIZATION OF HIV AND SARS-CoV-2 COINFECTION: ROLE OF IL-10

New Investigator Scholar

**Claudia Vanetti**[1], Daria Trabattoni[1], Marta Stracuzzi[1], Antonella Amendola[1], Clara Fappani[1], Valeria Rubinacci[1], Claudio Fenizia[1], Mara Biasin[1], Anna Dighera[1], Irma Saulle[1], Francesco Ardizzone[1], Elisabetta Tanzi[1], Mario Clerici[1], Gian V. Zuccotti[1], Vania Giacomet[1]
*[1]Università degli Studi di Milano, Milan, Italy*

**Background:** Interaction between HIV and SARS-CoV-2 infection has not yet been fully characterized. To this purpose, an in-vitro HIV/SARS-CoV-2 coinfection assay was set up. Furthermore, the results obtained in the in-vitro model were verified in a cohort of HIV/SARS-CoV-2 coinfected young individuals.

**Methods:** We designed an in-vitro SARS-CoV-2/HIV coinfection. We challenged PBMCs derived from 10 healthy volunteers with 1 ng/1×$10_6$ cells of HIV-1BaL and subsequently co-cultured them with a human lung epithelial cell line (CaLu3) infected with SARS-CoV-2 at 0.015 MOI. At 96 hours post HIV-1 infection, both PBMCs and CaLu3 cells were harvested for mRNA expression and proteomic analysis. Furthermore, we enrolled 85 ART-treated HIV-vertically transmitted patients (mean age 22.4 years) followed at the Unit of Pediatric Infectious Diseases, Sacco Hospital in Milan, Italy. Real−time PCR was performed to detect SARS-CoV-2 and plasma samples were tested for anti-SARS-CoV-2-specific IgG (Euroimmun Kit). The subjects who contracted SARS-CoV-2 infection (H+/S+) were compared to the HIV-positive, SARS-CoV-2 negative ones (H+/S-) and to a cohort of SARS-CoV-2 positive, HIV-negative age-matched patients (H-/S+, mean age 22.8 years). We evaluated mRNA expression of factors involved in the anti-viral immune response on PBMCs upon stimulation with SARS-CoV-2 antigens (Quantigene Plex assay) and secreted cytokines/chemokines on plasma (Multiplex Cytokine Array).

**Results:** We observed a significant reduction of SARS-CoV-2 replication on CaLu3 cells when exposed to HIV-pre-infected PBMCs in-vitro. IL-10 expression and production were significantly higher in the coinfected condition, in both CaLu3 cells and PBMCs. The upregulation of IL-10 was associated to higher expression levels of STAT3. In the HIV-vertically transmitted cohort, 4 out of 85 subjects contracted SARS-CoV-2 infection (H+/S+). All H+/S+ patients were asymptomatic. Similarly to the data obtained in-vitro, a significant increase in both expression and production of IL-10 emerged in comparison to H+/S- and H-/S+.

**Conclusion:** In-vitro, a dampening in SARS-CoV-2 replication, along with a higher IL-10 mRNA expression and production, have been observed in the HIV/SARS-CoV-2 coinfected condition. Presumably, IL-10 exerted its activity through the STAT3 pathway. These results were confirmed in HIV/SARS-CoV-2 coinfected subjects in which an upregulation of IL-10 was observed. Our data might be useful defining HIV/SARS-CoV-2 coinfected young individuals pathogenesis.

## 175 CHARACTERIZING MECHANISMS OF TRANSCRIPTIONAL CONTROL IN HIV-INFECTED MACROPHAGES

**Rachel Van Duyne**[1], Stephanie Matt[1], Alexis Brantly[1], Michael R. Nonnemacher[1], Peter J. Gaskill[1], Zachary A. Klase[1]
*[1]Drexel College of Medicine, Philadelphia, PA, USA*

**Background:** The presence of viral reservoirs resulting from HIV transcriptional latency is a major barrier to curing HIV, but research on HIV transcriptional latency has focused primarily on CD4+ T-cells. Significantly less work has been performed to examine HIV transcription in myeloid cells. Given the ability

of infected myeloid cells to survive for long periods of time and their role in mediating the inflammatory response our relative lack of understanding of transcriptional dynamics in these cells is a critical knowledge gap. It is unclear if infected myeloid cells experience transcriptional latency like CD4+ T-cells. The goal of this study was to determine the kinetics of HIV-1 transcription in human monocyte derived macrophages (hMDM) and the associated mechanisms.
**Methods:** hMDM were derived from PBMCs from healthy donors and inoculated with HIV-ADA. Virus replication in the presence or absence of antiretrovirals (ARVs) [bictegravir, tenofovir alafenamide, emtricitabine] was assayed by measuring supernatant p24 over time. Cells were collected to quantify cell-associated viral RNA and DNA, and to determine protein occupancy at the HIV LTR by ChIP. Infected cells at late replication timepoints were stimulated with latency reversal agents (LRAs) for 48 hrs followed by quantification of virus production.
**Results:** Supernatant p24 in hMDM infected with HIV-ADA or single-cycle virus HIV-RGH decreased by >80% within 6 days of ARV treatment but remained detectable. The number of infected cells, as measured by high content imaging of Gag expressing cells and qPCR for proviral genomes, was unchanged. RT-qPCR provided an overview of the transcriptional state at each time point. Treatment of infected, ARV-treated hMDM cultures with a panel of known T-cell LRAs failed to re-activate viral production.
**Conclusion:** These results suggest that hMDM produce large amounts of virus soon after infection but then produce less over time. This suggests a wildfire-like model of myeloid infection; the fire (viral production) is hottest at the start of the burn (newly infected cells), and then the hottest areas move with the edge of the fire, leaving behind cooler, less active embers (chronically infected cells). The inability of known LRAs to reactivate chronically infected macrophages supports the possibility that transcriptional control in myeloid cells is mechanistically distinct from T-cell latency. These differences will need to be considered when designing therapies to address the persistent reservoir.

**176 WITHDRAWN**

**177 SPECIFIC DETECTION AND REPLICATION KINETICS OF SARS-CoV-2 USING smRNA-FISH**

**Rajiv Pathak**[1], Carolina Eliscovich[1], Updesh Dixit[1], Nacho Mena[2], Adolfo Garcia-Sastre[2], James M. Pullman[3], Robert H. Singer[1], Ganjam V. Kalpana[1]
*[1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [3]Montefiore Medical Center, Bronx, NY, USA*

**Background:** SARS-CoV-2 is a positive-sense single-stranded RNA virus and its replication begins after the synthesis of virally encoded polymerase complex that is required for replication and transcription of genomic RNA (gRNA) within the infected cells. Despite the global interest in the study of SARS-CoV-2, the kinetics of SARS-CoV2 RNA replication and transcription during the early phase of viral infection is poorly understood. Here, we used the single-molecule RNA fluorescence in situ hybridization (smRNA-FISH) for sensitive detection of SARS-CoV-2 at single molecule level and to determine the replication of genomic RNA (gRNA) and sub-genomic RNA (sgRNA) in the infected cells, at very early stages of infection.
**Methods:** We designed highly specific smRNA-FISH probes targeted to gRNA and Spike gene sgRNA of SARS-CoV-2 virus, using stellaris method and optimized the method to simultaneously visualize these two RNAs at single cell and single molecule level. Because of the high sensitivity of our probes, we applied smRNA-FISH technology to detect SARS-CoV-2 positive cells from autopsy samples obtained from diseased COVID-19 patients. Furthermore, we used high-resolution and high-speed scanning microscopy to detect extent of infection in cell models of SARS-CoV-2 and in COVID-19 patient samples.
**Results:** A time course analysis SARS-CoV-2 replication indicated that single molecules of gRNA could be detected as little as 30 min to 2 hr. post-infection. Distinct "Replication Centers" (RC) began to appear one to two hours post-infection and the sgRNAs began to migrate out of these RCs. Replication after the initial delay appeared to be rapid and gRNA and sgRNAs dispersed throughout the cell within 4-5 hours post infection forming multiple RCs. We found that our RNA-FISH correctly detected the SARS-CoV-2 positive samples from patient autopsy samples that were characterized by qRT-PCR or immunological detection methods. The signals of spike gRNA and sgRNA along with the spike proteins co-localized within the same cells of the SARS-CoV-2 infected patients within the cells of lung, kidney, and heart autopsy samples.
**Conclusion:** We propose that the specific probes and the methodology that we have developed will be highly applicable to the study of SARS-CoV-2 replication in depth and to characterize SARS-CoV-2 infection in COVID-19 patient samples. This study may open a novel direction towards COVID-19 pathophysiology, drug screening and diagnostics.

**178 QUANTIFYING SARS-CoV-2 INFECTION KINETICS FROM UNVACCINATED AND VACCINATED PERSONS**

**Ruian Ke**[1], Pamela Martinez[2], Rebecca L. Smith[2], Christopher B. Brooke[2]
*[1]Los Alamos National Laboratory, Los Alamos, NM, USA, [2]University of Illinois Urbana-Champaign, Urbana, IL, USA*

**Background:** Transmission of SARS-CoV-2 is highly heterogeneous, with a small fraction of infected individuals (often referred to as "superspreaders") contributing a disproportionate share of forward transmission. Numerous behavioral and environmental explanations have been offered to explain transmission heterogeneity, but the extent to which the underlying features of the infection process within individual hosts contribute towards the superspreading phenomenon remains unclear. In addition, it is not clear how vaccination would impact on the viral infection dynamics and thus the infectiousness of individuals. Addressing these gaps in knowledge will inform the design of more targeted and effective strategies for controlling community spread.
**Methods:** In a study on UIUC campus (UIUC SHIELD), the dynamics of infectious virus and viral RNA shedding were captured through daily longitudinal sampling of 72 individuals for up to 14 days (60 unvaccinated and 12 vaccinated). We fitted mechanistic models to both viral loads and cell culture positivity data, and directly estimated viral reproduction and clearance rates, and overall infectiousness for each individual.
**Results:** Integrating mathematical models with viral load and cell culture positivity data, we show a substantial level of heterogeneity in infectiousness of individual. In unvaccinated individuals, peak viral loads and clearance kinetics of B.1.1.7 and non-variant of concern viruses were indistinguishable. In vaccinated individuals, the viral dynamics do not follow typical patterns of acute infection

dynamics and we estimate that these individuals are much less infectious than unvaccinated individuals.
**Conclusion:** Our work provides a high-resolution portrait of SARS-CoV-2 infection dynamics. Significant person-to-person variation in infectious virus shedding suggests that individual-level heterogeneity in viral dynamics contributes to superspreading. Vaccinated individuals are less infectious than unvaccinated individuals overall.

### 179 MUTATIONS IN PERSISTENT SARS-CoV-2 CASES

**Lacy M. Simons**[1], Judd F. Hultquist[1], Ramon Lorenzo-Redondo[1], Egon A. Ozer[1], Michael G. Ison[1], Chad J. Achenbach[1]
[1]*Northwestern University, Chicago, IL, USA*

**Background:** The evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants with decreased susceptibility to neutralizing antibodies are of clinical importance. While several demographic and clinical correlates of Coronavirus Disease 2019 (COVID-19) outcome have been identified, their relationship to virological and immunological parameters remain poorly defined. Here, we evaluate viral diversity and the accumulation of intra-host mutations over time in a population of hospitalized adults positive for SARS-CoV-2.
**Methods:** We performed longitudinal collection of nasopharyngeal swabs and blood samples from a small cohort of hospitalized adults with COVID-19. Clinical information regarding study subject's immunocompromised status was collected. Samples were assessed for SARS-CoV-2 viral load, viral genotype, viral diversity, and antibody titer.
**Results:** Intra-host viral genetic diversity remained constant through disease course in study subjects that were non-immunocompromised and resulted in changes in viral genotype in some participants. We report the de novo emergence of Spike mutations that have been previously associated with circulating variants of concern in two immunosuppressed patients with persistent SARS-CoV-2 infection.
**Conclusion:** Constant rates of viral evolution suggest the emergence of variants as a function of time, emphasizing the need for effective antivirals to control viral load over long disease courses.

### 180 ORF1 REGION OF SARS-COV-2 GENOMIC RNA AS A PROMISING TARGET FOR siRNA-BASED THERAPY

New Investigator Scholar

**Shubhankar Ambike**[1], Cho-Chin Cheng[1], Martin Feuerherd[1], Domizia Baldassi[2], Stoyan Velkov[1], Gerald Burgstaller[2], Olivia M. Merkel[2], Thomas Michler[1]
[1]*Technical University of Munich, Munich, Germany,* [2]*University of Munich, Munich, Germany*

**Background:** A promising approach to tackle the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) could be small interfering (si)RNAs. However, it is unclear so far, which viral replication steps can be efficiently inhibited with siRNAs. Here we report the first-ever in-depth analysis of RNAi-accessible SARS-CoV-2 replication steps.
**Methods:** siRNAs were designed against four genomic regions of SARS-CoV-2. Initial screening of siRNA activity was performed with a dual luciferase reporter assay. Efficacy of siRNAs to terminate various viral replication steps was analyzed by infecting VeroE6 cells with wildtype SARS-CoV-2 or a GFP expressing recombinant SARS-CoV-2 and monitoring viral spread in real-time by time-lapse fluorescence microscopy. Positive and negative sense viral RNA transcripts were distinctly quantified via sense specific cDNA synthesis and reverse-transcriptase quantitative PCR. Finally, the antiviral activity of the siRNAs was primarily evaluated in a highly relevant model, SARS-CoV-2 infected human lung explants.
**Results:** When applied in a prophylactic fashion, siRNAs were able to target genomic RNA (gRNA) of SARS-CoV-2 after cell entry, terminating replication before start of transcription, thereby preventing cytopathic effects. Surprisingly, siRNAs were not active against intermediate negative sense transcripts formed during replication. Targeting sequences that are commonly shared by all viral transcripts indeed allowed a simultaneous suppression of gRNA and subgenomic (sg)RNAs by a single siRNA. However, siRNAs that targeted ORF1 which is solely part of gRNA, presented an enhanced antiviral activity. We show that the reason for this was that siRNAs that targeted the common regions of transcripts were outcompeted by the highly abundant sgRNAs. Based on these findings, we developed a chemically stabilized siRNA, which targets a highly conserved region of ORF1, and which inhibited SARS-CoV-2 replication by >90% ex vivo in explants of the human lung.
**Conclusion:** Our work strongly encourages the development of siRNA-based therapies for COVID-19 and suggests that early therapy start, or prophylactic application, together with targeting ORF1, might be key for high antiviral efficacy.

### 181 ROLE OF ACTIN REGULATORS IN HIV-1, IAV, & SARS-CoV-2 VIRUS-LIKE PARTICLES PRODUCTION

New Investigator Scholar

**Manon Gourdelier**[1], Peggy Merida[1], Jitendriya Swain[1], Delphine Muriaux[1]
[1]*Institut de Recherche en Infectiologie de Montpellier, Montpellier, France*

**Background:** Human immunodeficiency virus (HIV) and Influenza A virus (IAV) remain a global health concern. Further, emergence of novel coronavirus SARS-CoV-2, which rapidly became global pandemic, increases the concern in biomedical research field for antiviral treatment. To develop new antiviral therapy, we must need to understand the molecular and cellular mechanisms involved in assembly and replication. It is known for some viruses (HIV and IAV) that the host actin cytoskeleton has been involved in various stages of the virus life cycle. Regulation of actin cytoskeleton requires several actin binding proteins, which organize the actin filaments (F-actin) into higher order structures such as actin bundles, branches, filopodia and microvilli, for further assistance in viral particle production. Thus, our objective for this work is to understand the role of these actin regulator proteins, like cofilin and one of its cofactor WDR1, in viral particle assembly and release.
**Methods:** Here we used a combination of different experimental methods like RNA interference, immunoblot, immunoprecipitation, immunofluorescence coupled to confocal and STED fluorescence microscopy. In order to study only virus release, and bypass viral entry, we set up a minimal system for virus-like particles production in transfected cells, giving HIV-1 Gag-VLP, Influenza M1-VLP and SARS-CoV-2 MNE-VLP (developed by D. Muriaux lab). For image analysis, we used Image J software. Statistical analysis was performed with non-parametric t-tests or one-way Anova test.
**Results:** Using siRNA strategy, we have shown that upon knock down of actin protein cofilin or WDR1, HIV-1 and IAV particles production increases in contrario to SARS-CoV-2 VLP release. Further, using immunoprecipitation, we report that HIV-1 Gag is able to form an intracellular complex with WDR1 and cofilin. Similarly, IAV-M1, which like HIV Gag-MA binds with plasma membrane phospholipids, is able to form an intracellular complex with cofilin. These results suggested that virus budding from the host cell plasma membrane seemed restricted by the cofilin/WDR1 complex. Finally, using confocal/STED microscopy on cell producing VLP, we observed actin fibers rearrangement with cell protrusions, suggesting a role for actin in viral particles assembly and release.
**Conclusion:** In conclusion, regulators of actin dynamic are involved in HIV-1 Gag, IAV-M1 and SARS-CoV-2 VLP production but play a differential role in assembly and release of these RNA enveloped viruses.

### 182 REDUCING HIV-1 HXB2 env GENE CpG FREQUENCY INCREASES VIRUS REPLICATION CAPACITY

**Ana Jordan-Paiz**[1], Sandra Franco[1], Miguel A. Martinez[1]
[1]*IrsiCaixa Institute for AIDS Research, Badalona, Spain*

**Background:** Synonymous replacement of CpG dinucleotides in the HIV-1 envelope (env) coding region has been correlated with evasion of the antiviral activity of the zinc-finger antiviral protein (ZAP). We aimed to explore the effect of depleting HIV-1 env CpG dinucleotides by synonymous substitution on ex vivo viral replication capacity. To this end, we eliminated 11 env CpG dinucleotides through synonymous substitutions in the HIV-1 CXCR4-tropic HXB2 strain.
**Methods:** HIV-1 HXB2 virus was engineered by PCR to synonymously deplete 11 env CpGs. After recovering and titrating the mutant virus, we performed replication kinetics experiments with both the variant and WT viruses to determine the relative replication capacity of the variant carrying the CpG-depleted env gene. These kinetic experiments were performed in MT-4 cells and PBMCs from healthy donors. To measure viral replication differences more accurately, dual infections of WT and variant viruses were also performed in MT-4 cells.
**Results:** The replication kinetics in MT-4 cells and PBMCs of the WT and synonymously recoded mutant viruses were indistinguishable. However, virus competition assays in MT4 cells between the WT and recoded viruses showed that the mutant with fewer CpG dinucleotides quickly overgrew the WT virus. Remarkably, of the 11 CpG dinucleotides we removed, 8 are located in gp120 and 3 in gp41. Since there are 8 CpGs in WT HXB2 gp120, the substitutions removed all the CpG dinucleotides in this env coding region, including the 4 CpG residues

located in the first 700 bases at the 5´ end of env. The number of CpGs among these 700 bases is known to determine the ZAP sensitivity of HIV-1, and thus impacts virus viability. These results demonstrate that a reduction in HIV-1 env CpG dinucleotide frequency can improve viral replication capacity in cell culture. This finding extends prior work regarding the impact of env CpG dinucleotide frequency on virus viability and fitness.

**Conclusion:** We confirmed the relevance of CpG frequency in the 5´ sequence of the env gp120 coding region on HIV-1 replication capacity. Our results support the previous observation that the frequency of CpGs in the HIV-1 env region correlates with differences in clinical progression rates in infected individuals.

## 183 UNRAVELING THE ANTIVIRAL ACTIVITY OF PLITIDEPSIN BY ULTRASTRUCTURAL ANALYSIS

**Martin Sachse**[1], Raquel Tenorio[1], Isabel Fernández de Castro[1], Jordana Muñoz-Basagoiti[2], Daniel Perez-Zsolt[2], Alejandro Losada[3], Pablo Avilés[3], Carmen Cuevas[3], Roger Paredes[2], Joaquim Segalés[4], Bonaventura Clotet[2], Júlia Vergara-Alert[5], Nuria Izquierdo-Useros[2], Cristina Risco[1]

*[1]Centro Nacional de Biotecnología, CSIC, Madrid, Spain, [2]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [3]PharmaMar, Madrid, Spain, [4]UAB, CReSA (IRTA-UAB), Barcelona, Spain, [5]IRTA, Centre de Recerca en Sanitat Animal (CReSA, IRTA-UAB), Barcelona, Spain*

**Background:** The use of compounds against highly conserved cellular host factors required to complete the replication cycle of distinct viruses such as SARS-CoV-2 offers a common solution to diverse viral threats. This approach is especially relevant for pan-antiviral effects given that viruses converge at intracellular steps such as viral genome replication and protein production. Currently, there are only a limited number of approved drugs involved in targeting intracellular host factors. One of these compounds is plitidiepsin, which has shown a potent preclinical efficacy against SARS-CoV-2 by targeting the host protein eEF1A. Plitidepsin inhibits nucleocapsid viral protein expression and viral induced cytopathic effect in vitro. In addition, it also reduces genomic and subgenomic RNA expression. However, how plitidepsin exerts its antiviral activity remains unknown.

**Methods:** Current models of SARS-CoV-2 replication propose that upon viral fusion, non-structural viral proteins form a replication–transcription complex that associates to compartments with a double membrane vesicle (DMV) morphology that shelters the viral genome replication. Here we have used an electron microcopy analysis to explore the antiviral effect of plitidepsin and its impact on SARS-CoV-2 replication and DMV formation on target Vero E6 cells.

**Results:** This ultrastructural analysis allowed to recapitulate the SARS-CoV-2 infectious life cycle, where evident viral DMV formation was observed as well as viral budding events along with cell-associated viruses. However, in cells treated with plitidepsin at different non-toxic concentrations (0.2 and 0.05 µM) there was a lack of viral DMV formation and a complete absence of viral particles. Complementary SARS-CoV-2 nucleocapsid and dsRNA immunogold labelling unambiguously confirmed the lack of viral replication in plitidepsin-treated cells. Overall, these data indicate that plitidepsin treatment abrogated the formation of DMVs, and the detection of nucleocapsid or dsRNA viral products.

**Conclusion:** Electron microscopy ultrastructural analysis coupled to immunogold labelling of SARS-CoV-2 products offer a unique approach to understand how antivirals work. This knowledge is key to identify the mechanism of action of promising compounds interfering with host factors whose implication in strategic biological processes can be applied as pan-antiviral strategies.

## 184 REPURPOSING SINGLE-CELL RNA SEQ DATA TO QUANTIFY HIV SPLICING DURING LATENCY REVERSAL

**Ann L. Emery**[1], Jackson Peterson[1], Edward P. Browne[1], Ronald Swanstrom[1]

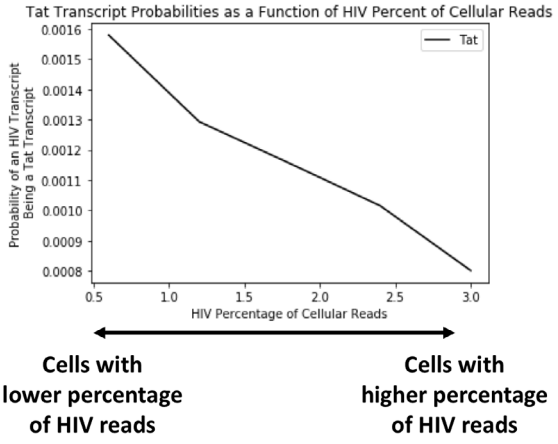
*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** Causes of HIV latency are incompletely understood. One theory is that low levels of Tat or Rev transcripts play a role. If Tat transcripts were insufficient to produce adequate Tat protein, transcription would tend to abort. Insufficient Rev would result in a functional latency by preventing export of unspliced and partially spliced HIV mRNAs. If a downward spiral of Tat or Rev transcripts were crucial in establishing and maintaining latency, we would expect latent cells to be less likely to carry out the splicing events required to produce Tat or Rev transcripts.

**Methods:** Our analysis used 10x Genomics single cell RNAseq data from a primary cell model of HIV latency. Cells in this study were all initially verified as actively HIV infected, but over time tended to become quiescent/latent and expressed a wide range of HIV transcript levels at the time of sequencing. 10x single cell seq tags each poly-A transcript with a barcode unique to each cell and an ID tag unique to each transcript. In principle this targets only mRNA 3' ends, yet we found that HIV transcripts primed across the entire A-rich genome, allowing identification of specific transcript types based on location and splicing activity. Although any one cell lacks sufficient HIV reads to determine expression patterns, we binned the cells into categories based on the percentage of HIV transcripts in the cell. We observed clear patterns of HIV transcript changes as cells went from low to high HIV expression. These changes were validated on a second single cell data set from a chemically activated latent cell line.

**Results:** Unspliced transcript levels increased uniformly from cells with low proportions of HIV reads to cells with high proportions of HIV reads. Conversely, levels of all spliced transcripts decreased as HIV reads/cell increased, for a net loss of 15% across expression levels analyzed. Tat and Rev transcripts decreased with a net loss of 50%. Thus HIV transcription during latency reversal is as seen in acute infection.

**Conclusion:** Unintended priming in the production of single cell sequencing libraries is a rich source of additional information about HIV transcript types, splicing activity, and changes in relative abundance of specific transcripts across a range of HIV transcriptional activation states. Our results show that a low cellular level of HIV transcripts increases the probability than any given HIV transcript will be a Tat or Rev transcript, which does not favor the theory of a Tat/Rev induced latency.




## 185 HYDROGEN SULFIDE BLOCKS HIV REBOUND BY MAINTAINING CELLULAR REDOX HOMEOSTASIS

**Virender K. Pal**[1], Ragini Agrawal[1], Amit Singh[1]

*[1]Indian Institute of Science, Bangalore, India*

**Background:** Understanding the mechanism of the establishment of HIV latency and its maintenance under antiretroviral treatment (ART) is of utmost importance. Previous studies suggest that the latent reservoir of HIV (monocytes and T cells) have elevated levels of redox buffers (eg, glutathione [GSH] and thioredoxin [Trx]) and antioxidant enzymes (superoxide dismutase, catalase, peroxidase). Moreover, the role of GSH and Trx in maintaining viral latency is extensively studied in the HIV field. In this study, we have discovered an unexpected role of the ubiquitous gasotransmitter molecule hydrogen sulfide (H2S) in modulating HIV latency and reactivation.

**Methods:** Levels of H2S biogenesis machinery were examined upon HIV latency and reactivation by RT-qPCR and western blotting. The efficacy of H2S releasing donor, GYY4137, on HIV reactivation was assessed using latent cell line models and primary CD4+ T cells derived from ART-treated HIV infected patients. The mechanism of H2S gas mediated effect on HIV reactivation was studied using NanoString based analysis of selected host genes, assessing mitochondrial functions by Seahorse XF assays, and monitoring cellular redox status with redox-active fluorescent dyes

**Results:** Our H2S biogenesis gene expression analysis showed that HIV reactivation is associated with the down-regulation of the key H2S producing enzyme cystathionine-γ-lyase (CTH) and reduction in endogenous H2S gas levels. Consistent with this, shRNA-mediated silencing of CTH results in

disruption of redox homeostasis, defective mitochondrial function, oxidation/depletion of cellular GSH, and remodels the transcriptome of latent cells to trigger HIV reactivation. Importantly, exogenous addition of H2S donor, GYY4137, in combination with ART subverted HIV rebound in latently infected primary CD4+ T cells derived from ART-treated HIV infected patients, raising the possibility of locking provirus in a deep-latent state by H2S based therapeutic interventions. Mechanistically, GYY4137 treatment subverted HIV reactivation by inducing the Keap1-Nrf2 dependent antioxidant pathway, inhibiting NF-κB activity, and recruiting the epigenetic silencer, YY1, to the HIV promoter.
**Conclusion:** In summary, this work provides mechanistic insight into H2S-mediated suppression of HIV reactivation and suggests the inclusion of an H2S donor in the current ART regimen to achieve a functional HIV cure.

## 186 DEFECTIVE RNA-DIRECTED STRAND DISPLACEMENT DUE TO HIV-1 RIBONUCLEASE H INACTIVATION

New Investigator Scholar

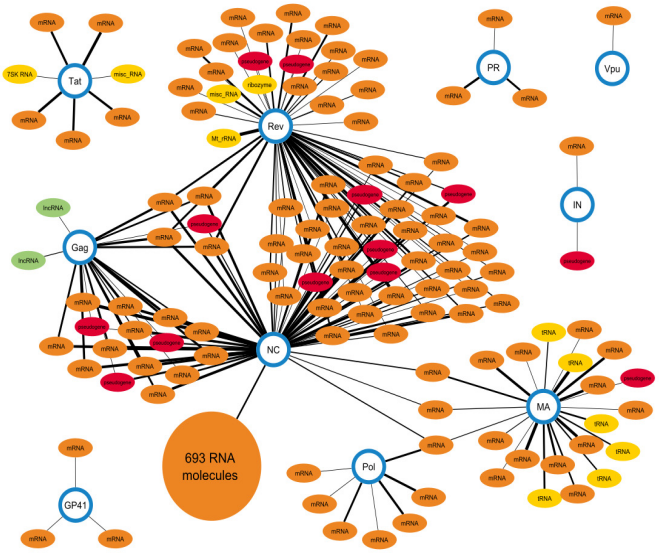
**Samara Martín Alonso**[1], Dongwei Kang[2], Javier Martínez del Río[1], Joanna Luczkowiak[1], Çağıl Urhan[1], Estrella Frutos Beltrán[1], Xinyong Liu[2], Peng Zhan[2], Luis Menéndez Arias[1]
*[1]Centro de Biología Molecular Severo Ochoa, Madrid, Spain, [2]School of Pharmaceutical Sciences, Shandong University, Ji'nan, China*

**Background:** In retroviruses, strand displacement DNA-dependent DNA synthesis catalyzed by the viral reverse transcriptase (RT) is required to obtain double-stranded proviral DNA. Strand displacement facilitates the elimination of uncleaved genomic RNA fragments during plus-strand DNA synthesis. In addition, strand displacement during RNA-dependent DNA synthesis is critical to generate high-quality cDNA for use in a variety of biotechnological applications.
**Methods:** Wild-type (WT) HIV-1BH10 RT and mutant RTs deficient in ribonuclease (RNase) H activity (carrying the substitutions D443N or E478Q) were tested in strand displacement DNA synthesis assays, in the absence or presence of RNase H active site inhibitors. RTs were expressed as heterodimers and purified by ionic exchange chromatography and metal-affinity chromatography. Control DNA synthesis reactions were carried out with RNA/DNA and DNA/DNA template-primers (54/17-mers), while strand displacement complexes included an additional displaced-oligonucleotide of 42 bases complementary to the 5' sequence of the template.
**Results:** After screening a panel of purified HIV-1 RTs, we identified several mutants with reduced strand displacement activity while copying RNA and DNA templates. The loss of RNase H activity due to inactivating mutations in HIV-1 (eg, D443N or E478Q) had a minimal effect on strand displacement when copying DNA templates. However, we observed a remarkable reduction in DNA polymerization if reactions were carried out with RNA templates. Similar results were obtained when using β-thujaplicinol, an RNase H active site inhibitor. Interestingly, the inhibitory effects observed with β-thujaplicinol in RNA-dependent DNA polymerization under strand displacement conditions were further confirmed using a panel of RNase H active site inhibitors obtained and previously characterized in our laboratories. Among them, dual inhibitors of the HIV-1 RT's RNase H and DNA polymerase activities, containing a 7-hydroxy-6-nitro-2H-chromen-2-one pharmacophore, were the most potent inhibitors of RNA-dependent strand displacement activity.
**Conclusion:** Our results demonstrate that the loss of RNase H activity reduces the efficiency of RNA-directed strand displacement DNA synthesis by HIV-1 RTs. These findings are expected to be helpful to design novel strategies to inhibit HIV reverse transcription while improving transcriptomics technologies aimed to obtain more uniform read coverages when copying long RNAs.

## 187 INTERACTOME OF HIV PROTEINS AND THEIR HOST RNA INTERACTION PARTNERS

**Tinus Schynkel**[1], W. J. Van Snippenberg[1], Kimberly Verniers[1], Eric J. de Bony de Lavergne[1], Gwendolyn M. Jang[2], Nevan J. Krogan[2], Pieter Mestdagh[1], Linos Vandekerckhove[1], Wim Trypsteen[1]
*[1]Ghent University, Ghent, Belgium, [2]University of California San Francisco, San Francisco, CA, USA*

**Background:** The HIV genome encodes a limited set of proteins, depending heavily on the exploitation of host cell molecules to complete its viral life cycle. Recent findings show that HIV hijacks cellular (non-coding) RNA molecules to aid in these crucial viral replication processes. Therefore, this study aims to systematically determine this new layer of physical interactions of each of the 18 HIV proteins with host RNA molecules.
**Methods:** For this purpose, an RNA immunoprecipitation (RIP)-seq strategy was established in Jurkat cell lines that express a single FLAG-tagged HIV protein upon doxycycline induction. For each of the 18 HIV proteins, FLAG-based immunoprecipitations (IP) were performed (triplicate), followed by RNA purification, stranded total RNA library preparation and sequencing (50M reads/sample, Illumina NextSeq). Background controls included an IP with a mouse IgG antibody and a FLAG-based IP on a Jurkat cell line that expressed a FLAG-tagged GFP protein. Enriched RNA transcripts were identified after mapping (STAR), background filtering based on IgG and GFP conditions and performing a differential expression analysis (DEseq2).
**Results:** The identified interactome comprises a set of 1116 HIV protein – host RNA interactions (FC > 4 and padj < 0.05) across 10 HIV proteins with Nucleocapsid displaying the highest RNA binding capacity with 984 interactions. The remaining 132 specific interaction were detected for Rev (65), Gag (22), Matrix (22), Pol (7), Tat (7), gp41 (3), Protease (3), Integrase (2) and Vpu (1). The majority of the identified RNA interaction partners are mRNAs (76%), and also include pseudogenes (19%) and (long) non-coding RNA molecules (5%), indicating a wide variety of RNA families that are recruited during replication. Furthermore, this interactome corroborates previous work, as known interactors were identified for Matrix (tRNAs) and Tat (7SKRNA). For Tat in specific, additional RNA interaction partners include mRNAs for which the translation protein products are known interactors of Tat within the super elongation complex (SEC). These Tat interactions were validated by Tat IP in the context of HIV infection, hinting at a regulatory role of Tat in the expression of these SEC subunits.
**Conclusion:** This unique and comprehensive dataset of HIV protein–human RNA interactions broadens our understanding on how HIV manipulates the RNA component of the host's cellular machinery during the course of infection and can be mined to investigate potential new therapeutic strategies.




## 188 VIRAL AND IMMUNE PREDICTORS OF TIME TO VIRAL REBOUND IN SHIV-INFECTED INFANT MACAQUES

**Veronica Obregon-Perko**[1], Achal Awasthi[2], Richard Barfield[2], Stella J. Berendam[3], Bhrugu Yagnik[4], Fan Bu[2], Tiffany M. Styles[4], Mithra R. Kumar[5], Emily J. Fray[5], Janet Siliciano[5], Rama R. Amara[4], Genevieve Fouda[3], Sallie Permar[3], Cliburn Chan[2], Ann Chahroudi[1]
*[1]Emory University, Atlanta, GA, USA, [2]Duke University School of Medicine, Durham, NC, USA, [3]Duke Human Vaccine Institute, Durham, NC, USA, [4]Yerkes National Primate Research Center, Atlanta, GA, USA, [5]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** Breastfeeding transmission remains a leading cause of pediatric HIV infections worldwide. Uncovering predictors of time to viral rebound (TTR) in a preclinical breastfeeding transmission model could identify clinical biomarkers to guide remission strategies and clinical trial design.
**Methods:** At 4 wks of age, rhesus macaques (RMs) were orally infected with SHIV.C.CH505.375H.dCT and placed on daily ART at 4-7 dpi (Early, n=10), 2 wpi (Intermediate, n=10), or 8 wpi (Late, n=10). Analytical treatment interruption (ATI) was performed after 1 yr. Peripheral blood (PB), lymph nodes (LN), and

rectal biopsies (RB) were collected for viral and immune (cellular and humoral) measures. The Cox Proportional Hazards model with LASSO regularization was used to identify and rank parameters that predicted TTR. Variables were pruned for multi-linearity using a Pearson correlation cutoff of 0.9. Leave-one-out Cross Validation (LOOCV) deviance, the error of a fitted model in predicting out-of-sample data points, was used for selection of predictor variables.

**Results:** Viral rebound occurred in 26/30 infant RMs within 7-98 d of ATI, with TTR significantly delayed in the Early ART group ($p<0.001$) compared to the Intermediate and Late ART groups (median TTR 84, 18, and 17 d post-ATI, respectively). Intact SHIV genome levels were undetectable in PB and LN CD4+ T cells prior to ATI in 10/10 Early ART animals. Reservoir burden pre-ATI was comparable between Intermediate and Late ART groups (median 6 and 17 intact genomes/million CD4+ T cells, respectively). Through multivariate regression modeling of 82 variables, we constructed a predictor inclusion rank table where peak plasma viral load best described TTR (LOOCV deviance 4.03), with the strength of predictions increasing with successive inclusion of pre-ART SHIV RNA in PB CD4+ T cells and pre-ATI levels of CD69+Perf+ NK cells, intact SHIV genomes in LN CD4+ T cells, SHIV DNA in RB CD4+ T cells, GzmB+ CD8+ T cells, and ADCP (LOOCV deviance 3.69). Individually, peak plasma viral load and PB CD4+ T cell SHIV RNA were associated with accelerated TTR (HR 1.63 and 1.23, respectively), whereas GzmB+ CD8+ T cells were associated with delayed TTR (HR 0.81).

**Conclusion:** This work provides novel insight into predictors of TTR in a preclinical NHP model of pediatric HIV-1 infection. Predictors identified in our model should be explored further to determine if they can serve as readily-measurable biomarkers to screen children with HIV-1 being considered for ATI.

## 189 IMPACT OF CD4 BINDING SITE bNAbs ON BARCODED TF-SHIV-D REBOUND IN MACAQUES AT ATI

New Investigator Scholar

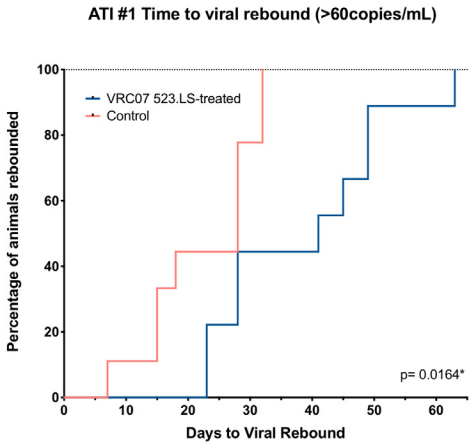
**Elise G. Viox**[1], Sadia Samer[2], Kevin Nguyen[1], Emily Lindemuth[3], Felicity Mampe[3], Steffen Docken[4], Mykola Pinkevych[4], M. Betina Pampena[3], Brandon Keele[5], Michael Betts[3], Miles P. Davenport[4], Mirko Paiardini[1], Katharine J. Bar[3]
*[1]Emory University, Atlanta, GA, USA, [2]Northwestern University, Chicago, IL, USA, [3]University of Pennsylvania, Philadelphia, PA, USA, [4]University of New South Wales, Sydney, Australia, [5]AIDS and Cancer Virus Program, Frederick, MD, USA*

**Background:** HIV bNAb therapies have been demonstrated to suppress viral rebound following analytical treatment interruption (ATI) in multiple clinical trials. Here, we utilized a novel barcoded transmitted/founder (TF)-SHIV to characterize the effects of CD4 binding-site (CD4bs) bNAb therapy on a diverse latent pool at ATI in rhesus macaques (RMs).

**Methods:** 18 RMs were infected with barcoded TF-SHIV-D and initiated ART at 120 days post-infection that was maintained for 6 months. At ATI #1, 9 RMs received a single, 30mg/kg i.v. dose of VRC07.523.LS while the other 9 RMs remained untreated. ART was re-initiated 4 months after ATI #1, maintained for 6 months, and then interrupted for a second time. At ATI #2, all 18 RMs were treated with both 30mg/kg VRC07.523.LS and VRC01.LS. All RMs underwent elective necropsy 5 months after ATI #2. Blood was collected frequently following both ATIs to determine viral rebound kinetics. To characterize rebounding viral populations, high-throughput Illumina based sequencing on the barcode region was performed in parallel with 3' SGS of half genomes.

**Results:** Barcoded TF-SHIV-D-infected RMs established high peak plasma viral loads (average of 4.61E+06 copies/mL) and the very large majority of animals established robust set point viral loads, mimicking viral dynamics observed in humans. All 18 animals rebounded following ATI #1 and 17/18 rebounded after ATI #2, further validating barcoded TF-SHIV-D for persistence on ART and rebound after ATI. Time to viral rebound following ATI #1 was significantly delayed in VRC07.523.LS-treated as compared to untreated animals (median 41 vs. 28 days; $p=0.0164$). Viral sequencing revealed similar numbers of rebound lineages in VRC07.523.LS-treated and untreated controls at ATI#1 (median 2 (range 1-4) vs. 3 (range 1-7). A trend towards faster time to rebound following ATI #2 was observed in previously treated vs. untreated RMs (median 35 vs. 45 days), potentially due to archived VRC07.523.LS resistance. Comparing ATI #1 vs. #2, the 9 RMs that were untreated at ATI #1 experienced a more delayed time to viral rebound at ATI #2 with bNAb treatment ($p=0.0006$).

**Conclusion:** CD4bs bNAb monotherapy in barcoded TF-SHIV-D-infected RMs at ATI recapitulates key components of bNAb monotherapy in humans, including a modest but statistically significant delay in time to viral rebound. Thus, barcoded TF-SHIV-D infection in RMs is a promising predictive model for bNAb therapy and studying the mechanisms of viral escape from bNAb pressure.




## 190 DEVELOPMENT OF VIRAL BIOMARKERS IN SHIV INFECTED NONHUMAN PRIMATES

**Luca Sardo**[1], Guoxin Wu[1], Jessica Lewis[1], Carl J. Balibar[1], Paul Zuck[1], Daria Hazuda[1], Bonnie Howell[1]
*[1]Merck & Co, Inc, Kenilworth, NJ, USA*

**Background:** As HIV-1 infection has transformed from a fatal crisis into a chronic, life-long disease managed by anti-retroviral therapy (ART), attention has shifted towards curative therapies. A regimen which may allow for viral control off ART will likely require a combination of agents to address HIV reservoirs and induce immune control. These complex interactions are difficult to study in vitro and thus require access to in vivo models. Infection of Rhesus macaques with SIV or chimeric HIV allows study of viral pathogenesis, biomarkers, and emerging cure interventions. Here we describe efforts to apply in situ hybridization (ISH) and immunohistochemistry (IHC) imaging techniques, and ultrasensitive immunoassays (Simoa) to detect host and viral proteins and RNA in samples derived from infected non-human primates (NHPs).

**Methods:** We collected biological samples from lymph nodes (LNs), gut associated lymphoid tissue (GALT), and blood from a cohort of NHPs including uninfected and SHIV162p3-infected viremic and aviremic animals. We measured plasma viral loads by quantitative PCR (assay LOD<10^2 c/ml) and used Simoa to detect SIV-p27 in blood and tissues. Other tissue specimens were fixed, paraffin embedded, and subjected to microtomy for the detection of SIV-p27, viral RNA and follicular dendritic cells (FDCs) by ISH or IHC with commercially available reagents followed by computational image analysis.

**Results:** We detected SIV-RNA signal by ISH in LNs and GALT of animals with low to undetectable plasma viremia above the background of tissue from uninfected individuals. SIV-p27 IHC signal was detected in LNs of some animals with high viremia, but less efficiently in other tissue compartments and aviremic animals. LNs from animals with plasma viremia >10^3 c/ml presented co-compartmentalization of SIV-RNA and-p27 with FDCs. SIV-p27 measured by Simoa was not readily detected in blood cells but could be detected in rectal and jejunal biopsies of animals with higher viral loads.

**Conclusion:** Tissue SIV-RNA and p27 ISH/IHC markers quantification correlated in samples across the compartments tested. Using ISH/IHC, Simoa, and qPCR assays, we are assembling a set of biomarkers to investigate viral RNA and protein in NHPs with variable levels of viremia. These assays will also be multiplexed with host biomarkers to further characterize the microenvironments that sustain virus persistence and provide insights into the effectiveness of clearance of infected cells from tissues.

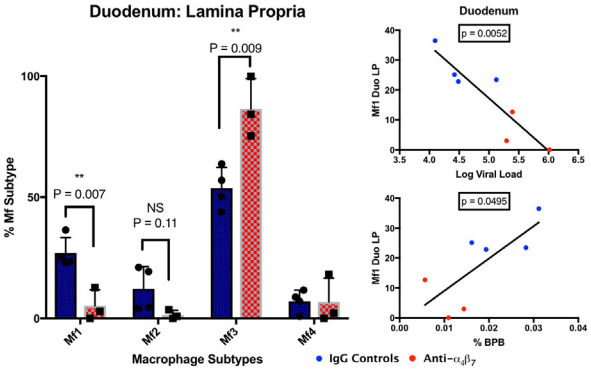
## 191 ANTI-A4B7 ANTIBODY REDUCES INTESTINAL MYELOID CELL TURNOVER IN SIV-INFECTED MACAQUES

New Investigator Scholar

**Samuel D. Johnson**[1], Lindsey Knight[2], Omalla Olwenyi[1], Michellie Thurman[1], Siddappa N. Byrareddy[1]
*[1]University of Nebraska Medical Center, Omaha, NE, USA, [2]University of Nebraska, Omaha, NE, USA*

**Background:** Despite advances in combination antiretroviral therapy (cART), HIV-infected individuals experience gastrointestinal symptoms and gut barrier dysfunction. Previous studies indicate anti-α4β7 integrin monoclonal antibodies (mAbs) reduce gut lymphoid aggregation in the gut and more recently, that they increased time to viral rebound when co-administered with

broadly neutralizing Abs in SIV-infected macaques. However, the impact of anti-α4β7 mAb on gut myeloid cells remains elusive.
**Methods:** Nine CD8-depleted rhesus macaques (Macaca mulatta) were infected with SIVmac251. At week 2, daily cART injections and infusions (anti-α4β7 mAb: n=5; IgG controls: n=4) every three weeks were initiated. The cART was discontinued at week 14, but infusions continued until week 23. At week 28, necropsies were performed. Gut immune cells were isolated, and Bujko's (2018) gating strategy was utilized to determine macrophage maturity from recently differentiated monocytes (Mf1) to mature lamina propria (Mf3) and muscularis (Mf4) macrophages. Further, fecal DNA was isolated, subjected to 16S rRNA sequencing, and the relative abundance of butyrate-producing bacteria (BPB) was determined by qPCR and tissue DNA viral loads were quantified with ddPCR.
**Results:** In the duodenum, Mf1 were lower (p=0.007) and Mf3 higher (p=0.009) in the anti-α4β7 group and Mf4 were higher (p<0.001) in the colon compared to controls. Independent of macrophage subset, CD103+ expression was lower on CD11c+ cells in the gut (together, p=0.003). BPB relative abundance was correlated with macrophage turnover (Mf1: r=0.7556, p=0.05; Mf3: r=-0.8646, p=0.01) and CD103 expression on CD11c+ cells (r=0.8037, p=0.03) in the duodenum. Duodenum viral loads were correlated with myeloid cells: (Mf1: r=0.8173, p=0.005; Mf3: r=0.6017, p=0.04, CD103+CD11c+: r=0.7213, p=0.02)
**Conclusion:** Vedolizumab reduces peripheral monocyte turnover and is more efficacious with BPB-enriched microbiomes. Here, we characterize macrophage turnover in the gut and correlate it with BPB abundance and viral loads during anti-α4β7 therapy. Gut macrophage turnover is associated with accelerated pathogenesis in SIV-infected macaques, and CD11c+CD103+ dendritic cells orchestrate gut trafficking. By inhibiting these processes, anti-α4β7 may improve outcomes and reduce inflammatory lymphocyte infiltration. These findings implicate the microbiome-immune crosstalk as a novel factor in viral reservoir formation and anti-α4β7 efficacy studies.




## 192 INNATE IMPAIRMENT DURING SIV INFECTION ALTERS ZIKV VIRAL PATHOGENESIS

**Jennifer Tisoncik-Go**[1], Thomas B. Lewis[1], Skyler Groenier[1], Daniel Newhouse[1], Kathleen M. Voss[1], Erin Broderick[1], Karina Wang[1], Naoto Iwayama[2], Chul Ahrens[2], Robert Murnane[2], Kathryn A. Guerriero[2], Michael Gale[1], Deborah H. Fuller[1], Megan A. O'Connor[1]
*[1]University of Washington, Seattle, WA, USA, [2]Washington National Primate Research Center, Seattle, WA, USA*

**Background:** Flaviviruses are in >100 countries across the globe and in areas with endemic HIV. Despite the occurrence of large flavivirus outbreaks and geographic overlap in countries with high HIV prevalence, there is insufficient research to determine the risks of flavivirus co-infection in people living with HIV and impact on co-morbidities. Here, in SIV-infected pigtail macaques, we investigated the hypothesis that enhanced ZIKV pathogenesis occurs in people living with HIV.
**Methods:** Pigtail macaques (n=7) were infected with SIVmac239M and co-infected with ZIKV at 9 weeks post-SIV infection (SIV+/ZIKV+). Animals were compared to control animals (n=7) only infected with ZIKV (SIV-/ZIKV+). SIV and ZIKV viral loads in plasma and peripheral tissues were measured by qRT-PCR. Blood/peripheral blood mononuclear cells (PBMCs), lymph node, and rectal tissues collected pre- and post-SIV and/or ZIKV infection were evaluated for innate and adaptive immune responses by flow cytometry. Alterations in host responses were measured in PBMC using NanoString gene analysis.
**Results:** At the time of ZIKV co-infection, SIV+ animals had severe CD4 depletion and an average viral setpoint of 5.6 $log_{10}$ SIV copies/ml of plasma. ZIKV viremia was detected on average for 2 days longer in SIV+/ZIKV+ animals in comparison to SIV-/ZIKV+ control animals and peak viremia was shifted on average 1.67 days later in SIV+/ZIKV+ animals. Post-ZIKV infection, peripheral recruitment of CD16+ monocytes, the in vivo blood target of ZIKV infection, was dampened and delayed in SIV+/ZIKV+ vs SIV-/ZIKV+ animals, and corresponded to the delayed ZIKV viremia in SIV+/ZIKV+ animals. Despite lower levels of CD16+ monocyte recruitment, SIV infection induced sustained activation of CD16+ monocytes during ZIKV co-infection. Furthermore, PBMC gene expression analysis post-ZIKV infection revealed hyperactivation of the innate immune response, including interferon alpha signaling, in SIV+/ZIKV+ animals.
**Conclusion:** Here, we provide evidence that ZIKV viremia is delayed in SIV-infected macaques, demonstrating a prolonged window of viral transmission. Characterization of the immune response revealed chronic activation of innate signaling pathways and innate immune activation, but impaired innate cellular recruitment responses during SIV-ZIKV co-infection. Collectively, these findings suggest that untreated SIV/HIV infection could create an environment of immunological tolerance that may lead to poor ZIKV viral clearance and promote pathogenesis.

## 193 SARS-CoV-2 SPIKE PROTEIN DESTABILIZES MICROVASCULAR HOMEOSTASIS

New Investigator Scholar

**Soumya Panigrahi**[1], Tamal Goswami[2], Brian Ferrari[1], Christopher J. Antonelli[1], Douglas A. Bazdar[1], Hannah Gilmore[1], Michael L. Freeman[1], Michael M. Lederman[1], Scott F. Sieg[1]
*[1]Case Western Reserve University, Cleveland, OH, USA, [2]Raiganj University, Raiganj, India*

**Background:** SARS-CoV-2 infection can compromise respiratory function and cause thrombotic events. SARS-CoV-2 binds to and mediates downregulation of angiotensin converting enzyme 2 (ACE2) on infected cells. Diminished enzymatic activity of ACE2 could result in increased concentrations of the pro-inflammatory molecules angiotensin II and bradykinin, contributing to SARS-CoV-2 pathology.
**Methods:** Immunofluorescence microscopy and digital image data quantification, Computer assisted molecular docking analyses, Western blot.
**Results:** Using immunofluorescence microscopy of lung tissues from uninfected and SARS-CoV-2 infected individuals, we find evidence that ACE2 is highly expressed in the pulmonary alveolar epithelium and is significantly reduced along the alveolar lining of SARS-CoV-2 infected lungs. Ex vivo analyses indicate that ACE2 is readily detected on primary human pulmonary alveolar epithelial and primary human aortic endothelial cells (HAoECs). Exposure of these cells to recombinant SARS-CoV-2 spike protein was sufficient to reduce surface ACE2 expression. Moreover, exposure of HAoECs to spike protein induced endothelial dysfunction (increased expression of von Willebrand Factor and decreased expression of Krüppel-like Factor 2), caspase activation, and apoptosis. Exposure of HAoECs to bradykinin (BK, 10μM) induced calcium signaling and endothelial dysfunction but did not adversely affect viability. Computer assisted analyses of molecules with potential to bind bradykinin receptor B2 (BKRB2) suggested a potential role for aspirin as a bradykinin antagonist. When tested in our in vitro model, we found that aspirin (1μM) could significantly blunt cell signaling, and endothelial dysfunction caused by bradykinin in these cells.
**Conclusion:** SARS-CoV-2 causes complex effects on microvascular homeostasis that potentially contribute to organ dysfunction and coagulopathies. Reduced ACE2 enzymatic activity could contribute to inflammation and pathology in the lung. Our studies add to this understanding by providing evidence that spike protein alone can mediate adverse effects on vascular cells. Understanding these mechanisms of pathogenesis may provide rationale for interventions, such as interference with the interactions of spike protein or bradykinin with endothelial cells, that could limit microvascular events associated with SARS-CoV-2 infection and stabilize microvascular homeostasis in COVID-19 disease.

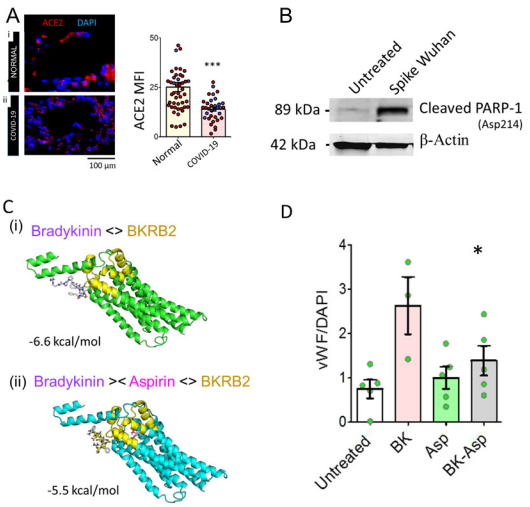



**Figure 1**: A. Surface expressions of ACE2 in normal and COVID-19 lung alveoli. Epi-fluorescent microscopy images, and quantification (n =10+4, p <0.001***). B. recombinant SARS-CoV-2 spike protein (Wuhan strain) trigger PARP-1(asp214) cleavage in endothelial cells (72 hrs, 100ng/ml, n = 3). C. Computer assisted molecular docking showing induced reduction of binding affinity of bradykinin (BK) to its receptor (BKRB2) in presence of Aspirin (Asp). D. Aspirin decreased BK induced endothelial dysfunction by down modulating Von Willebrand factor (vWF) (n > 300 cells, p= * <0.05).

## 194 UNIQUE SARS-CoV-2 FURIN-CLEAVAGE SITE VARIANTS IN URINE OF SEVERE COVID-19 PATIENTS

**Tatianna Travieso**[1], Sneha Mahesh[1], Kelly Hughes[1], Lingye Chen[2], Lyra B. Olson[3], Feng Gao[3], Bryan D. Kraft[3], Christina Wyatt[3], Mary Klotman[3], Maria Blasi[3]
*[1]Duke Human Vaccine Institute, Durham, NC, USA, [2]Duke University, Durham, NC, USA, [3]Duke University School of Medicine, Durham, NC, USA*

**Background:** Although the respiratory tract is the initial site of infection for SARS-CoV-2, coronavirus disease 19 (COVID-19) can affect multiple organ systems with devastating consequences. Acute kidney injury (AKI) has emerged as a leading cause of morbidity, affecting more than a third of adult patients hospitalized with COVID-19. SARS-CoV-2 infection is believed to cause AKI through different mechanisms, including interaction with the angiotensin-converting enzyme 2 (ACE2) receptor, cytokine storm, hemodynamic compromise, and direct viral infection of kidney cells. A major barrier to studying the kidney as a potential site of viral infection and replication is the limited availability of fresh kidney tissue from human subjects. To overcome this limitation, we assessed the presence of SARS-CoV-2 RNA in urine of critically ill COVID-19 patients.

**Methods:** Fifty-two sequential urine and nasal swab specimens were collected from 18 patients (median (IQR) age 57 (50-62) years) hospitalized in the intensive care unit (ICU) with COVID-19. We performed single genome amplification and sequence analysis of the full-length SARS-CoV-2 spike gene to determine the frequency of genetic mutations in urine compared to those amplified from nasal swabs.

**Results:** Forty single genome SARS-CoV-2 spike sequences were amplified in urine samples from four of the ten patients that developed AKI. Analysis of these sequences revealed that deletions and mutations of the SARS-CoV-2 furin-cleavage site (RRAR) were the predominant mutations observed in urine-derived viral RNA (30/40). For 3 of the 4 patients the corresponding nasal swabs were negative for SARS-CoV-2, suggesting that these patients were shedding viral RNA in urine but had cleared the infection in the respiratory tract. None of the 15 nasal swab sequences derived from the fourth patient had deletions or mutations in the furin-cleavage site.

**Conclusion:** Our study identified unique mutations/deletions in the SARS-CoV-2 spike gene amplified from urine samples of critically ill COVID-19 patients. Notably, these mutations/deletions have been infrequently observed in SARS-CoV-2 genome sequences from respiratory tract samples deposited in the publicly available databases but have been reported to occur after passaging the virus in the African green monkey kidney cell line, Vero-E6, raising the possibility of SARS-CoV-2 renal tropism or cell/organ specific selection of viral variants. Our data provide in vivo evidence of a phenomenon previously reported only in vitro.

## 195 GALECTIN-9 PROTECTS HUMANIZED ACE2-IMMUNOCOMPETENT MICE FROM SARS-CoV-2 INFECTION

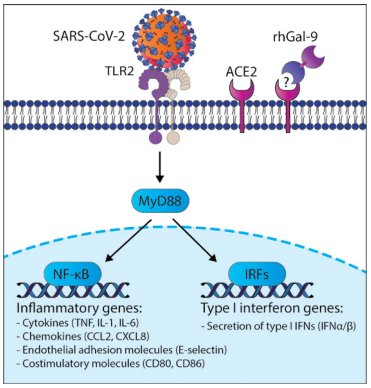
**Stephen T. Yeung**[1], Thomas A. Premeaux[1], Toshiro Niki[2], Satish Pillai[3], Kamal M. Khanna[4], Lishomwa Ndhlovu[1]
*[1]Weill Cornell Medicine, New York, NY, USA, [2]Kagawa University, Kagawa, Japan, [3]University of California San Francisco, San Francisco, CA, USA, [4]New York University Langone Medical Center, New York, NY, USA*

**Background:** Coronavirus disease 2019 (COVID19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) remains a global health emergency even with effective vaccines and limited FDA-approved therapies. To limit mortality and morbidity across the spectrum of disease, the need for therapeutics remains critical. Galectin9 (gal9) is a beta-galactoside binding protein that modulates cell-cell and cell-matrix interactions. In response to SARS-CoV2 infection, it has been shown that circulating gal9 levels are elevated in patient sera with moderate to severe disease. Additionally, it has been reported that gal9 unexpectedly may competitively bind the host ACE2 receptor, potentially impeding viral entry. Therefore, we hypothesized that early recombinant gal-9 treatment post infection may prevent binding of the virus to susceptible host cells resulting in decreased severity of SARS-CoV2-associated disease.

**Methods:** To determine the therapeutic potential of gal9 for treating COVID19, we infected K18-hACE2 transgenic mice intranasally with 10^4 particle forming units (PFU) of SARS-CoV2. 6 hours post infection (hpi), mice were treated with a single dose of 30 ug of recombinant human gal9 (rhgal9) or PBS intraperitoneally and subsequently monitored 12 days for morbidity. Subgroups of mice were humanely euthanized at 2 and 5 days pi (dpi) for viral plaque assay, flow cytometry, and protein analysis from lung tissue and bronchial alveolar lavage (BAL).

**Results:** We found that mice treated with rhgal9 during the acute phase of infection exhibit improved survival compared to PBS treated animals (25%, $p<0.0001$). We found that at 5 dpi, rhgal9 treated mice exhibited enhanced viral clearance in the BAL but not in the lung parenchyma. Additionally, we found increased CD8 T cell ($p<0.001$) and decreased neutrophil ($p<0.05$) frequencies in the lung at 5 dpi. Finally, we found that BAL fluid had elevated levels of Type 1 Interferon [IFNa ($p<0.01$) and IFNb ($p<0.01$)] at 2 dpi and increased MyD88 proinflammatory cytokines [IL1a ($p<0.05$), IL1b ($p<0.01$), TNFa ($p<0.05$), and MIP1a ($p<0.05$) at 5 dpi.

**Conclusion:** Our study suggests that rhgal9 treatment may be potentially therapeutic for treating acute COVID19. Our data suggest that rhgal9 treatment in combination with other anti-inflammatory mediators may curtail damaging inflammation associated with SARS-CoV2 disease. Further studies are required to determine the optimal time, combination and duration of treatment pi to effectively target the gal9 pathways.




## 196 SARS-CoV-2 PLASMA VIREMIA AND DYSREGULATED IMMUNITY IN SEVERE COVID-19

New Investigator Scholar

**Roberta Rovito**[1], Valeria Bono[1], Matteo Augello[1], Camilla Tincati[1], Federica Mainoldi[2], Guillaume Beaudoin-Bussières[3], Silvia Bianchi[1], Mohamad Hadla[1], Vaibhav Yellenki[1], Stefano Casola[2], Elisa Borghi[1], Andrés Finzi[3], Antonella D'Arminio Monforte[1], Giulia Marchetti[1]
*[1]University of Milan, Milan, Italy, [2]FIRC Institute of Molecular Oncology (IFOM), Milan, Italy, [3]Centre de Recherche du CHUM, Montreal, Canada*

**Background:** Critical COVID-19 occurs ca. 7d from symptoms onset, and is associated to immune dysregulation as well as SARS-CoV-2 detection in plasma

(i.e. viremia). We hereby sought to detail the association between SARS-CoV-2 viremia measured at the end of the first week of disease and immune phenotypes/function in COVID-19 patients.

**Methods:** We consecutively enrolled patients hospitalized in the acute phase of ascertained SARS-CoV-2 pneumonia. In this disease stage, we studied SARS-CoV-2 viremia (RT-PCR) and cytokines (MACSPlex), HLA-DR+CD38+ activated, GRZB+PRF+ pro-cytolitic T-cells, intracellular cytokine production (IL-2, IFNγ, TNFα, IL-4, IL-17A) after SARS-CoV-2 challenge (S-N-M-peptide pool). Simultaneous Th1-cytokines production (polyfunctionality) and amount (iMFI) was assessed. Humoral response: anti-S1/S2 IgG, anti-RBD total-Ig, IgM, IgA, IgG1 and IgG3 (ELISA), pseudoviruses neutralization (ID50) and Fc-mediated functions (%ADCC).

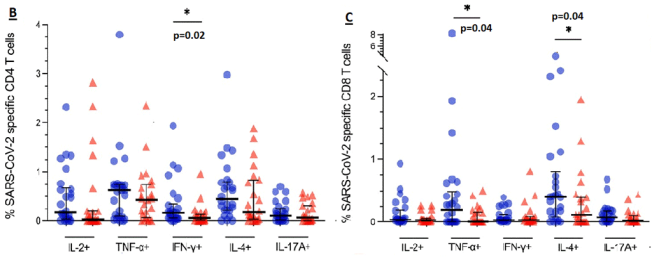
**Results:** Out of 54 patients, 27 had detectable viremia (V+). Albeit comparable age and co-morbidities, V+ patients more frequently required non-invasive/invasive ventilatory support (p=0.035), with a trend to higher death (p=0.099) vs patients with undetectable viremia (V-)(Fig.1A). V+ displayed higher circulating IFN-α (p=0.002) and IL-6 (0.003), lower activated HLA-DR+CD38+CD4 (p=0.01) and CD8 (p=0.02), with no differences in GRZB+PRF+ T-cells. V+ featured reduced SARS-CoV-2-specific cytokine-producing T-cells, reaching significance for IFNγ+CD4 (p=0.02), TNFα+CD8, IL-4+CD8 (p=0.04) (Fig.1B-C), with lower bi- and tri-functional SARS-CoV-2-specific CD4 Th1, reaching significance for IL-2+TNFα+CD4 (p=0.03) (Fig.1D). A trend towards lower cytokines iMFI in bi- and tri-functional SARS-CoV-2-specific CD4 Th1 was observed in V+, reaching significance for IL-2+TNFα+CD4, p=0.004. V+ displayed lower anti-S IgG, anti-RBD total-Ig, IgM, IgG1 and IgG3 (Fig.1E), with lower ID50 and %ADCC vs V-(Fig.1F-G).

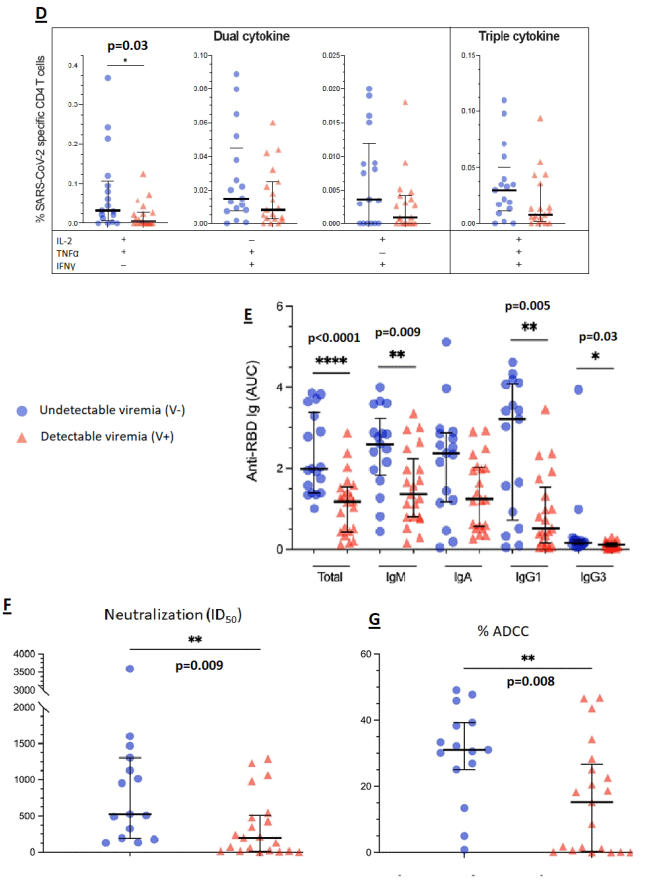
**Conclusion:** Hospitalized COVID-19 patients with detectable plasma SARS-CoV-2 RNA in the acute phase of disease present worse outcome, higher inflammatory cytokines, fewer activated and SARS-CoV-2-specific polyfunctional T-cells, suggesting a link between SARS-CoV-2 viremia at the end of the first stage of disease and immune dysregulation. Whether high ab initium viral burden and/or intrinsic host factors contribute to a delayed and/or exhausted immune response in severe COVID-19 remains to be elucidated, to further inform strategies of targeted therapeutic interventions.

**Figure 1. SARS-CoV-2 SPECIFIC T-CELL AND ANTIBODY RESPONSE ACCORDING TO VIREMIA**

**A**

| Demographic and clinical characteristics | ALL PATIENTS (n=54) | V+ (n=27) | V- (n=27) | *p*-value V+ vs V- ° |
|---|---|---|---|---|
| **Sex**, n (%) | | | | >0.9999 |
| Male | 39 (72.2) | 20 (74.1) | 19 (70.4) | |
| Female | 15 (27.8) | 7 (25.9) | 8 (29.6) | |
| **Age, years**, median (IQR) | 64 (52.50–75.25) | 67 (55–78) | 63 (45–71) | 0.1659 |
| **Comorbidities**, n (%) | | | | |
| Any comorbidity | 29 (53.7) | 16 (59.3) | 13 (48.2) | 0.5857 |
| Hypertension | 20 (37) | 10 (37) | 10 (37) | >0.9999 |
| Myocardial infarction | 8 (14.8) | 6 (22.2) | 2 (7.4) | 0.2501 |
| Cardiac arrhythmia | 3 (5.6) | 1 (3.7) | 2 (7.4) | >0.9999 |
| COPD | 1 (1.9) | 1 (3.7) | 0 (0) | >0.9999 |
| Asthma | 2 (3.7) | 0 (0) | 2 (7.4) | 0.4906 |
| Peptic ulcer | 2 (3.7) | 0 (0) | 2 (7.4) | 0.4906 |
| Chronic kidney disease | 2 (3.7) | 2 (7.4) | 0 (0) | 0.4960 |
| Diabetes | 14 (25.9) | 9 (33.3) | 5 (18.5) | 0.3520 |
| Stroke | 3 (5.6) | 1 (3.7) | 2 (7.4) | >0.9999 |
| Dementia | 1 (1.9) | 0 (0) | 1 (3.7) | >0.9999 |
| Cancer | 2 (3.7) | 2 (7.4) | 0 (0) | 0.4960 |
| Rheumatologic disease | 1 (1.9) | 0 (0) | 1 (3.7) | >0.9999 |
| **Duration of symptoms before hospitalization, days**, median (IQR) | 7 (4–10) | 7 (4–10) | 6 (4–14) | 0.4099 |
| **Maximum oxygen therapy**, n (%) | 6 (11.1) | 1 (3.7) | 5 (18.5) | 0.1917 |
| None | 10 (18.5) | 3 (11.1) | 7 (25.9) | 0.2935 |
| Low/high-flow systems CPAP/NIV/OTI | 38 (70.4) | 23 (85.2) | 15 (55.6) | **0.0352** |
| **Duration of hospitalization, days**, median (IQR) | 14.50 (6–25) | 20 (8–28) | 13 (6 –22) | 0.4258 |
| **Outcome**, n (%) | | | | 0.0994 |
| Death | 12 (22.2) | 9 (33.3) | 3 (11.1) | |
| Dismissal | 42 (77.8) | 18 (66.7) | 24 (88.9) | |




**RBD:** Receptor-Binding Domain of SARS-CoV-2 Spike; **% ADCC:** anti-SARS-CoV-2 antibody-dependent cellular cytotoxicity; **Neutralization ($ID_{50}$):** plasma dilution to inhibit 50% of cellular infection by pseudoviruses. Statistical analyses: Mann-whitney test; plots: median and IQR; GraphPad Prism 9.
* Statistical analyses: Fisher exact test or Mann-Whitney U test; IQR: interquartile range;
CPAP: continuous positive airway pressure; NIV: noninvasive ventilation; OTI: orotracheal intubation.

## 197 SARS-CoV-2 N-ANTIGEN SERA LEVELS ARE ASSOCIATED WITH COVID-19 PROGNOSTIC VALUE

**Houssem R. Chenane**[1], Reyene Menidjel[1], Samuel Lebourgeois[1], Cedric Louenan[2], Sarah Tubiana[2], Diane Descamps[2], Laurent Abel[3], Jérémie Guedj[1], Surbhi Malhotra[4], Samir Kumar-Singh[4], Jade Ghosn[2], Benoît Visseaux[2]
*[1]INSERM, Paris, France, [2]Assistance Publique–Hôpitaux de Paris, Paris, France, [3]Unidad de Investigación en Tuberculosis de Barcelona, Barcelona, Spain, [4]University of Antwerp, Antwerp, Belgium*

**Background:** Small studies have reported that high levels of free SARS-CoV-2 nucleocapsid-antigen in sera (N-antigenemia) was associated with prognostic. Here, we assessed the association between N-antigenemia levels and patient's outcome in a large cohort of hospitalized patients.

**Methods:** We analysed data from patients with at least one sera sample that were included in the French COVID cohort between January, 25 2020 and September, 2 2020. N-antigenemia levels were determined with the COV-Quanto® assay (AAZ) with a limit of detection of 2.98 pg/mL. IgG (anti-N, anti-S and anti-RBD) levels were assessed using the V-PLEX panel assay (MSD). Patient's outcome was classified in three groups: death, recovery with ICU transfer (ICU) and recovery without ICU transfer (Hospital).

**Results:** We included 1166 samples from 357 patients, with 66% of male and a median age at 63 years [IQR: 52-71]. A total of 82, 96 and 142 patients were in the Death, ICU and Hospital groups, respectively. The sensitivity of N-antigenemia was 79% (131/165) within the first 10 days SSO (since symptoms onset) and 62% (365/589) from 11 to 30 days SSO. Positivity rates were significantly different across severity groups from 0 to 15 days SSO: 95% (95/100), 64% (118/183), 79% (83/105) (p<0.001) for Death, ICU and Hospital groups, respectively. Among positive patients, a significant gradient was found in the levels of N-antigenemia according to disease severity, with median levels of 302, 134 and 89 in Death, ICU and hospital groups, respectively. Similar relationships were found when stratifying on the time SSO (see figure). Overall, 95, 80, 43 and 22% of N-antigenemia >10,000, >5,000, >1,000 and <1,000 pg/

mL corresponded to patients who died. IgG antibodies titers were not correlated to severity and the presence of both sera N-antigen and anti-N IgG was observed for 42% (490/1166) samples.

**Conclusion:** We observed, on a large prospective cohort, a strong relationship between N-antigenemia and COVID-19 severity. This new diagnostic tool should help to prognostic evaluation of COVID-19 patients. To our knowledge, COVID-19 is the first demonstration of the presence of free antigenemia in a viral pneumonia, and its association with prognostic.

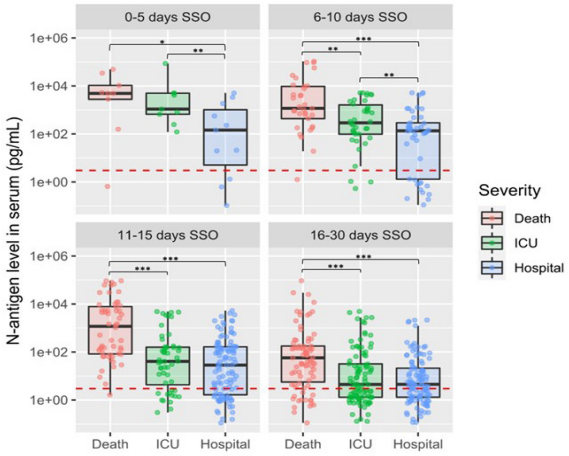



***Figure:*** N-antigenemia serum levels according to severity (Death, ICU and Hospital patients' groups) and time since symptoms onset (SSO). Manufacturer positivity threshold (2.98 pg/mL) is indicated by the red dashed line. Statistical significance between groups is indicated by asterisks (* p<0.05; ** p<0.025; *** p<0.001).

## 198 SARS-CoV-2 RNAEMIA AS A BIOMARKER OF LOWER RESPIRATORY VIRAL LOAD IN COVID-19

**Jana L. Jacobs**[1], Asma Naqvi[1], Faraaz A. Shah[1], Bryan J. McVerry[1], Barbara Methé[1], Janet S. Lee[1], Alison Morris[1], Georgios D. Kitsios[1], William Bain[1], John W. Mellors[1]

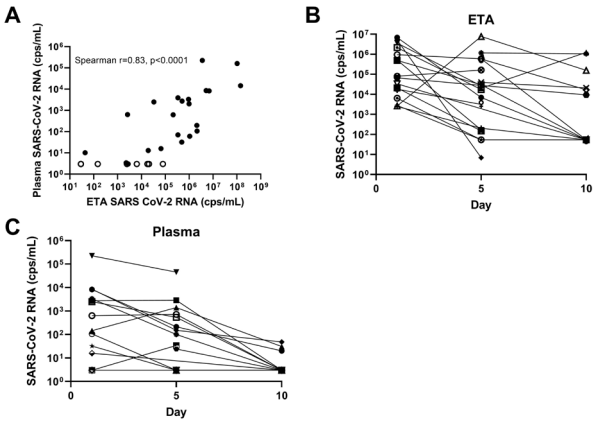
[1]*University of Pittsburgh, Pittsburgh, PA, USA*

**Background:** SARS-CoV-2 plasma RNAemia correlates strongly with COVID-19 severity and predicts clinical outcome, but how RNAemia levels relate to viral load in the lower respiratory tract has not been well-defined. Delineating the relationship of viral load in the lung and blood compartments in COVID-19 may help guide therapeutic interventions and could provide insight into the viral dynamics of these two compartments. Here we compared SARS-CoV-2 RNA levels in plasma to those in lower respiratory secretions.

**Methods:** We used an internally-controlled, ultrasensitive (1 copy/extraction) qRT-PCR assay for SARS-CoV-2 N gene RNA to test plasma and endotracheal aspirate (ETA) samples collected on the same day from mechanically-ventilated patients with COVID-19 prospectively enrolled from three hospitals in Pittsburgh. Samples were collected at enrollment on day 1 (D1), D5, and D10.

**Results:** SARS-CoV-2 RNA was detected in 22/33 (67%) plasma (median 32 cps/mL, IQR [<3-2608 cps/mL]) and 28/33 (85%) ETA samples (median 66,300 cps/mL, IQR [2395-1,028,500 cps/mL]) collected on D1. Of the 28 ETA samples with detectable SARS-CoV-2 RNA, 22 (79%) had detectable RNAemia. Viral RNA levels were more than 2,000-fold higher in ETA than plasma, but plasma and ETA viral RNA levels were strongly correlated (Spearman r=0.83, p<0.0001, Fig 1A). Viral RNA levels generally decreased concordantly over time in both plasma and ETA samples (Fig 1B and C).

**Conclusion:** SARS-CoV-2 viral RNA levels in plasma and lower respiratory tract secretions are strongly correlated in patients with severe COVID-19. This finding provides support for plasma viral RNA as a biomarker of lung infection, which could prove to be useful in guiding therapeutic interventions and monitoring response to therapies.




## 199 SARS-CoV-2–INFECTED MACAQUES EXHIBIT MICROBIAL TRANSLOCATION ACROSS INTESTINAL MUCOSA

**Kelsie Brooks**[1], Christine Nelson[1], Cynthia Aguilar[1], Charlotte Langner[1], Sophia Vrba[1], Alexandra Ortiz[1], Ornella Sortino[1], Kevin Vannella[1], Timothy Hoang[2], Mirko Paiardini[2], Daniel Chertow[1], Irini Sereti[1], Heather Hickman[1], Daniel Barber[1], Jason Brenchley[1]

[1]*National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA,* [2]*Yerkes National Primate Research Center, Atlanta, GA, USA*

**Background:** Gastrointestinal symptoms and viral RNA (vRNA) in stool have been described in human SARS-CoV-2 infections. However, intestinal pathology and related inflammation have not been extensively described in humans or animal models. Here we investigate the effect of SARS-CoV-2 infection on the gut mucosa and inflammation in rhesus macaques (RM) and humans.

**Methods:** Fourteen adult RM were infected with US/WA-1/2020 SARS-CoV-2 instilled intranasally and intratracheally. Animal clinical features (mass, temperature, etc.) and samples (nasal swabs, throat swabs, blood, stool, etc.) were collected at baseline and up to day 10 post-infection at necropsy. RNA was extracted from swab and stool samples and vRNA measured by qRT-PCR. Plasma samples were assessed for inflammatory biomarkers by ELISA. Tissues collected at necropsy were fixed and evaluated for microbial translocation through immunohistochemical (IHC) staining of bacterial products; H&E staining was also performed. Tissues were additionally collected from uninfected RM and processed in the same manner. Human plasma samples from individuals with moderate COVID-19 were collected at early infection and recovery time points and assessed for inflammatory biomarkers.

**Results:** SARS-CoV-2 infection of RM did not induce fever nor weight loss over five percent. vRNA was detected in all animals in nasal and throat swabs. vRNA, including subgenomic RNA indicative of viral replication, was also detected in stool samples. Scores for translocating bacteria in colon sections stained by IHC for bacterial products were higher for SARS-CoV-2 infected RM than uninfected controls. Additionally, follicles made up a higher percentage of total mesenteric lymph node area in SARS-CoV-2 infected animals than control RM. Furthermore, soluble CD14 in plasma increased significantly from baseline to day 10 of SARS-CoV-2 infection (p=0.0006) and decreased significantly in humans from early infection to recovery time points (p=0.0295).

**Conclusion:** Thus, adult RM experienced mild to moderate SARS-CoV-2 infections yet demonstrated evidence of microbial translocation. Humans similarly demonstrated evidence of microbial translocation that decreased upon recovery from COVID-19. These data suggest gut pathology in SARS-CoV-2 infection may be contributing to systemic inflammation in COVID-19.

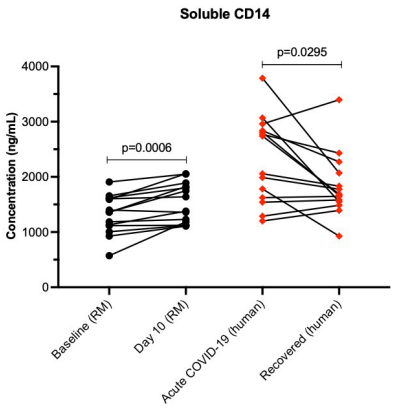



Figure: Plasma soluble CD14 values in RM and humans.
p-values for Wilcoxon matched-pairs signed rank test

## 200 PULMONARY CMV REACTIVATION FOLLOWING SARS-CoV-2: IMPLICATIONS FOR IMMUNOPATHOLOGY

Late Breaking

**Jamin Roh**[1], Peter A. Barry[1], Peter W. Hunt[2], Smita S. Iyer[1]
*[1]University of California Davis, Davis, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA*

**Background:** SARS-CoV-2 infection results in a spectrum of disease severity attributable to the magnitude of the underlying inflammatory response. Aged individuals with co-morbidities are most vulnerable and severely affected, but the mechanisms driving aberrant immune responses fueling SARS-CoV-2 immunopathology in this high-risk population are not fully elucidated. We hypothesized that asymptomatic CMV infection might exacerbate SARS-CoV-2 pathogenesis since its replication is both a cause and consequence of inflammation and appears to worsen oxygenation in critically ill patients (Limaye, JAMA, 2017). CMV-seropositivity was associated with increased hospitalization among people with SARS-CoV-2 infection (Shrock, Science, 2020). To begin to address this hypothesis, we utilized the rhesus macaque model of natural rhesus (Rh)CMV infection to investigate the extent to which SARS-CoV-2 induces CMV reactivation in the anatomic sites of SARS-CoV-2 pathology.
**Methods:** To assess CMV reactivation, eight aged, type 2 diabetic RhCMV-seropositive rhesus macaques (sera anti-CMV IgG: 300-1400 ng/ml) were infected with high-dose SARS-CoV-2 (2.5x10 6 PFU) and monitored for 7 days prior to euthanasia. Samples from the respiratory tract, intestinal tract, and blood were collected to assess viral and inflammatory dynamics in distinct tissue compartments.
**Results:** Following infection, SARS-CoV-2 replication was observed throughout the respiratory tract, which was associated with local and systemic inflammation and immune activation. Lung histopathological assessments revealed development of interstitial pneumonia with colocalization of SARS nucleocapsid protein within pneumocytes. qPCR assays targeting RhCMV gB showed CMV DNA within the caudal lung lobe (up to 10^3 CMV DNA copies/mg of tissue) in all animals at day 7, and the animal with the highest CMV DNA presented with the most profound clinical symptoms. Strikingly, CMV DNA copies strongly correlated with CD4 and CD8 T cell activation indices in blood and spleen ($r = 0.96$, $p < 0.001$). Additionally, we found RhCMV reactivation in the ileum, where high levels of ACE2 are reported.
**Conclusion:** SARS-CoV-2 infection of RhCMV-seropositive macaques results in CMV reactivation in the anatomic sites where SARS-CoV-2 causes pathology. Future experimental studies should address whether CMV reactivation exacerbates SARS-CoV-2 pathogenesis.

## 201 IDENTIFICATION OF KEY BIOMARKERS FOR THE PREDICTION OF CRITICAL COVID-19 OUTCOMES

New Investigator Scholar

**Laia Reverté Calvet**[1], Elena Yeregui Etxeberria[1], Monsterrat Olona Cabases[1], Maria José Buzón[2], Anna Martí[1], Frederic Gómez-Bertomeu[1], Teresa Auguet[1], Clara Benavent-Bofill[1], Carme Boqué[1], Ezequiel Ruiz-Mateos[3], Maria Teresa Mestre[1], Francesc Vidal[1], Joaquin Peraire[1], Anna Rull[1]
*[1]Hospital Universitario de Tarragona Joan XXIII, Tarragona, Spain, [2]Vall d'Hebron Research Institute, Barcelona, Spain, [3]Institute of Biomedicine of Seville, Sevilla, Spain*

**Background:** Understanding the role of crucial biomolecules and mechanistic pathways supporting coronavirus disease 2019 (COVID-19) pathophysiology is essential to handle the immune dysregulation and complications driven by uncontrolled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Thus, we evaluated the proteomics, metabolomics and lipidomics plasma profile in a well-characterized cohort of COVID-19 patients ranging from asymptomatic to critical illness.
**Methods:** This multicenter case-control study enrolled 273 adults with SARS-CoV-2 infection, confirmed by Polymerase chain reaction (PCR), who were recruited within the first 21 days of the infection during the first wave (March-May 2020) of COVID-19 pandemic. Participants were categorized into three groups of severity according to the inclusion criteria described in "Diagnosis and Treatment Protocol for COVID-19 Patients" and distributed as mild (n=77), severe (n=134) and critical (n=62). Serum profile of COVID-19 patients was characterized in the acute phase of the infection using a nontargeted multiomics approach. Univariate and multivariate analyses were performed to identify key molecules involved in critical COVID-19 and to evaluate their predictive power as biomarkers of COVID-19 severity.
**Results:** COVID-19 critically ill patients presented a well-differentiated blood pattern for severe disease. The multiomic analysis identified specific alterations in pathways linked to complement and coagulation cascades, platelet activation, cell adhesion, acute inflammation, energy production (Krebs cycle and Warburg effect), amino acid catabolism and lipid transport as hallmarks of critical COVID-19. A new biomarker panel including the combination of selected proteins, metabolites and lipids predicted with high accuracy the most adverse COVID-19 outcomes (AUC: 0.994, 85.9% specificity and 100% sensitivity).
**Conclusion:** The identification of predictive molecules related to critical COVID-19 outcomes provides a valuable tool for the rapid and efficient identification of clinical worsening in the early stage of SARS-CoV-2 infection. The association of a distinctive proteomic, metabolomic and lipidomic fingerprint with COVID-19 severity provides a better understanding of the immunopathogenesis and the host response to SARS-CoV-2 infection which could help in the identification of potential therapeutic targets.

## 202 MACHINE LEARNING ANALYSIS OF DNA METHYLATION IN COVID-19 DISEASE

**Scott Bowler**[1], Giorgos Papoutsoglou[2], Aristides Karanikas[2], Ioannis Tsamardinos[2], Michael J. Corley[1], Lishomwa Ndhlovu[1]
*[1]Weill Cornell Medicine, New York, NY, USA, [2]JADBio, Heraklion, Greece*

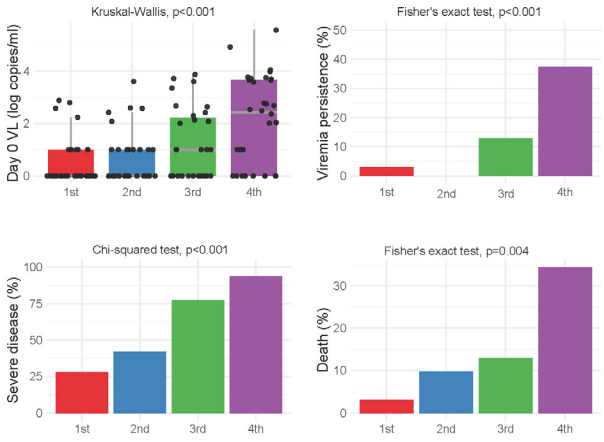
**Background:** SARS-CoV-2 infection has resulted in over 219 million confirmed cases of COVID-19 with 4.5 million fatalities, highlighting the importance of elucidating mechanisms of severe disease. Here we utilized machine learning (ML) technologies to identify DNA methylation footprints of COVID-19 disease from publicly available data.
**Methods:** Genome-wide DNA methylation of SARS-CoV-2 infected and uninfected patients using Illumina HumanMethylationEPIC microarray platform from whole blood was publicly available through NCBI Gene Expression Omnibus. A training cohort (GSE167202) consisting of 460 individuals (164 COVID-19-infected and 296 non-infected) and an external validation dataset (GSE174818) consisting of 128 individuals (102 COVID-19-infected and 26 non-COVID with pneumonia diagnosis) were obtained. COVID-19 severity score (SS) was classified as follows: 0. uninfected; 1. released from department to home; 2. admitted to in-patient care; 3. progressed to ICU; and 4. death. Participants were then dichotomized by SS=0 or SS≥3. Raw data was processed using ChAMP in R 4.1.1, resulting in over 850,000 methylation sites per sample for analysis. Beta values were logit transformed to M values using CpGTools in Python 3.8.8. JADBio AutoML platform was leveraged to analyze these datasets with the goal of identifying a methylation signature indicative of COVID-19 disease.

**Results:** From our training cohort, JADBio utilized LASSO feature selection (penalty=1.5) to identify 4 unique methylation sites capable of carrying the predictive weight of a classification random forest trained on 100 trees with Deviance splitting criterion (minimum leaf size=3). The average area under the curve of receiver operator characteristic (AUC-ROC) of the model was 0.933 (95% confidence interval [0.885, 0.970]), while the average area under the precision-recall curve (AUC-PRC) of 0.965 [0.932, 0.986]. When COVID-19 mild infections (SS = 1 or 2) were returned to the training dataset as an internal control, the model retained its predictive power (AUC-ROC=0.985, AUC-PRC=0.992). When applied to our external validation, this model produced an AUC-ROC of 0.901 with an AUC-PRC of 0.748.
**Conclusion:** We developed a Random Forest Classification model capable of accurately predicting COVID-19 infection leveraging JADBio AutoML platform. These results enhance our understanding of epigenetic mechanisms used by SARS-CoV-2 in disease pathogenesis and identify potential therapeutic targets.

## 203 IMMUNE EXHAUSTION IS ASSOCIATED WITH PERSISTENT SARS-CoV-2 VIREMIA AND SEVERE DISEASE

**Yijia Li**[1], Arnav Mehta[2], Matteo Gentili[2], Julian A. Villalba[3], Moshe Sade-Feldman[2], Kyle R. Kays[2], Nir Hacohen[2], Marcia B. Goldberg[3], Michael R. Filbin[3], Mari Mino-Kenudson[3], Jonathan Li[1]
*[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Broad Institute of MIT and Harvard, Cambridge, MA, USA, [3]Massachusetts General Hospital, Boston, MA, USA*

**Background:** SARS-CoV-2 viremia is associated with adverse outcomes in COVID-19. The immunologic mediators of this relationship remain under-explored. In this study, we aimed to evaluate the correlation between immune exhaustion markers, SARS-CoV-2 viremia clearance and clinical outcomes.
**Methods:** We included 126 participants with confirmed SARS-CoV-2 infection who were hospitalized at an urban hospital in Boston, Massachusetts, during the first surge of the COVID-19 pandemic in early 2020. Plasma samples from days 0, 3, and 7 of hospitalization were available for analyses. The plasma SARS-CoV-2 viral load was determined by reverse transcription quantitative PCR (RT-qPCR). Proteomics data were generated using the Olink platform and neutralization level was assessed using a pseudovirus neutralization assay. Viremia persistence was defined as >40 copies/ml (detection limit) if the baseline detectable viremia was <1000 copies/ml, or >100 copies/ml (quantification limit) if the baseline viremia was ≥1000 copies/ml at day 7 of admission. Partial least-squares discriminant analysis (PLS-DA) was used to select exhaustion markers that could distinguish viremia persistence and clearance. An exhaustion score was generated based on features selected by PLS-DA and was divided into four quartiles. Differentially expressed proteins between 1st and 4th quartiles were determined by linear model adjusting for baseline characteristics. R (4.1.0) was used for statistics.
**Results:** Viremia persistence was associated with a higher level of baseline viremia, a higher rate of severe diseases and mortality within 28 days of follow-up. Viremia persistence was associated with elevation of certain exhaustion protein markers including TIM3, PDL1, LGALS9, LAG3 and IL2RA. With PLS-DA, we selected TIM3, PDL1, and LGALS9 into the exhaustion score modeling. A higher exhaustion score was associated with higher baseline viremia, persistent viremia, severe disease, and death (Figure). When compared to the lowest exhaustion score (1st quartile), the highest exhaustion score (4th quartile) was associated with elevation in proteins belonging to IL-18 signaling pathway, lung fibrosis, and immune evasion in COVID-19. The immune exhaustion level was not associated with the neutralization level.
**Conclusion:** In participants with COVID-19, soluble exhaustion markers are associated with delayed viremia clearance, immune evasion independent of humoral immunity development, and adverse outcomes.




## 204 CIRCULATING LEVELS OF TYPE I, TYPE II, AND TYPE III INTERFERONS AND COVID-19 SEVERITY

**Alejandro A. Garcia**[1], Riya Negi[1], Camille Heckmann[2], Grace Kenny[1]
*[1]University College Dublin, Dublin, Ireland, [2]Côte d'Azur University, Nice, France*

**Background:** Interferons play a pivotal role as a first line of the innate immune host response to viral infections, including COVID-19. Accumulating data suggests dysregulated interferon (IFN) responses in COVID-19. However, the clinical relevance of circulating levels of interferon to COVID-19 disease severity remains unclear
**Methods:** In plasma from individuals with PCR confirmed SARS-CoV-2 infection recruited to the All Ireland Infectious Diseases Cohort, collected within 10 days from onset of symptoms, we measured levels of type I (IFN-α2a and IFN-β), type II (IFN-γ), and type III (IFN-λ1) interferons by electro-chemiluminescence immunoassays. Subsequent maximum COVID-19 disease severity was classified according to World Health Organization guidance (Critical, Severe, Moderate and Mild). We used Kruskal–Wallis tests to explore differences in IFN levels between COVID-19 severity groups, and logistic regression to determine associations, adjusting for demographics (age, sex at birth, ethnicity), comorbidities (obesity, hypertension, respiratory disease, heart disease) and medical management (antibiotics, immunosuppressants, anticoagulants, invasive ventilation)
**Results:** Out of the 335 subjects with early infection and available samples, 319 had data on disease severity, 33 (10.3%) Critical, 37 (11.6%) Severe, 76 (23.8%) Moderate and 173 (54.2%) Mild. The population was predominantly Caucasian (79.3%), with a median [IQR] age of 64 [53,77] and male (52.7%). There was a significant difference between the 4 groups for the levels of Type I IFN-α2a (p=0.0028) and Type 3 IFN-λ1 (p=0.0001), both being higher in the critical group. In adjusted analyses, higher levels of Type I IFN-α2a but not Type 3 IFN-λ1 remained significantly associated with the development of Critical COVID-19 (Odds Ratio: 5.911 / 95% CI: 0.608, 52.388 / p=0.029). (Fig 1)
**Conclusion:** Increased circulating Type I IFN-α2a, but not other IFN classes, measured in the early stages of SARS-CoV-2 infection was associated with higher odds of Critical COVID-19 infection. These data point to specific differences in host responses that may lead to more targeted interventions to prevent development of severe COVID-19 infection.

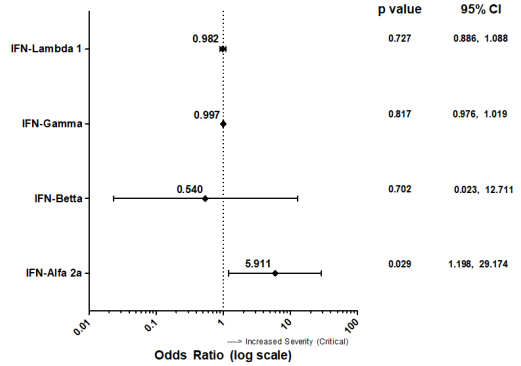



Fig 1. Forest Plot: Association between the interferons and a Critical COVID-19 disease status. Adjusted for demographics (age, sex at birth, ethnicity), comorbidities (obesity, hypertension, respiratory disease, heart disease) and medical management (antibiotics, immunosuppressants, anticoagulants, invasive ventilation). Odds Ratios, p-values and 95% confidence are shown for the 4 Interferons. Type I (IFN-α2a and IFN-β), type II (IFN-γ), and type III (IFN-λ1).

## 205 TGF-B2 IS ASSOCIATED WITH ASYMPTOMATIC/MILD SARS-CoV-2 INFECTION DURING PREGNANCY

**Rachel Pope**[1], Muhammad B. Latif[2], Gabriela Pacheco Sanchez[2], Meredith Gardner[3], Ruth Farrell[4], Kelly Gibson[5], Sarah O'Connell[6], Suprabhath Gajjaia[6], Adrian McDermott[6], Robert Balderas[7], Michael Konstan[8], Mehul Suthar[3], Rafick-Pierre Sékaly[2], Susan Pereira Ribeiro[2]

*[1]University Hospitals Urology Institute, Cleveland, OH, USA, [2]Emory University, Atlanta, GA, USA, [3]Yerkes National Primate Research Center, Atlanta, GA, USA, [4]Cleveland Clinic, Cleveland, OH, USA, [5]MetroHealth Medical Center, Cleveland, OH, USA, [6]National Institute of Allergy and Infectious Diseases Vaccine Research Center, Bethesda, MD, USA, [7]Beckton Dickson Biosciences, San Diego, CA, USA, [8]Case Western Reserve University, Cleveland, OH, USA*

**Background:** COVID-19 has been a devastating disease and a major public health concern mainly to susceptible populations.

**Methods:** We accessed two groups of pregnant women at the time of delivery: SARS-CoV2 active infection and convalescents. To investigate the factors contributing to COVID19 severity we have assessed several immunological parameters including cytokines/chemokine levels in the maternal and cord blood plasma. We have evaluated 33 cytokines. Our findings were validated in vitro in HTBE (Human tracheobronchial epithelial) cells infected with live SARS-COV2 (wild type).

**Results:** Our cohort was enriched in high-risk subjects, including African American and obese women. Only 6% had severe or critical disease, contrasting with the 20-25% reported in some pregnant cohorts. TGFb2 levels were significantly associated with asymptomatic/mild disease in both active and convalescent cohorts, and inversely correlated with IP10, IL6 and IL8, known to be part of the cytokine storm post-infection. Pre-treatment of HTBE with TGFb2 for 48 hours led to a significant decay in viral loads at 72h post-infection. This control was associated with significantly higher IL-6 (IFNb2) levels prior to infection, and significantly higher expression of anti-viral genes at 72h pi (MX1, IFNA1, IFNA2, IFNL1, STAT1). Additionally, TGFb2 pre-treatment suppressed the expression of the cytokines IP-10, IL1b and IL8.

**Conclusion:** Altogether this data suggested that TGFB2 plays a protective role in SARS-COV2 infection in this high-risk population by improving epithelial cells intrinsic antiviral function and by modulating the expression of the cytokines associated to the heightened inflammation in severe cases.

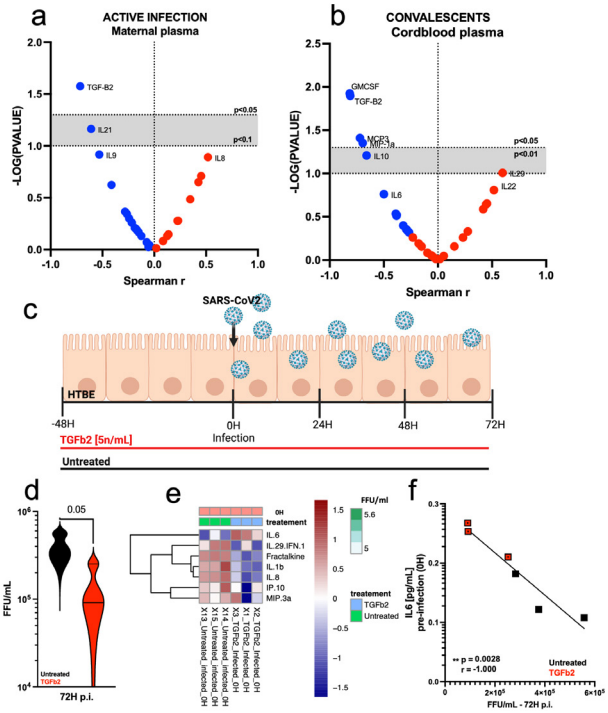



Fig 1. TGFb2 plasma levels were inversely correlated to COVID19 severe symptoms in pregnant women at active (**a**) and convalescent stages (**b**). **c**) Pre-treatment (48h) of HTBE cells with TGFb2 led to **d**) decay in viral load 72h post-infection. TGFb2 pre-treatment led to the upregulation of IL-6 (pre-infection 0h), and suppressed the expression of IL1b, IL8 and IP10 known to be associated to cytokine storm in the severe disease (**e**). IL-6 levels at 0h was inversely correlated to viral load at 72h p.i. (**f**).

## 206 GDF-15 AS A PREDICTOR OF MORTALITY IN COVID-19: IMPLICATIONS FOR TREATMENT

New Investigator Scholar

**Valeria Bono**[1], Paola Ciceri[1], Matteo Sala[1], Lorenza Magagnoli[1], Roberta Rovito[1], Luisa Artioli[1], Mohamad Hadla[1], Vaibhav Yellenki[1], Antonella D'Arminio Monforte[1], Andrea Galassi[1], Camilla Tincati[1], Giulia Marchetti[1], Mario Cozzolino[1]

*[1]University of Milan, Milan, Italy*

**Background:** A cytokine storm drives the pathogenesis of severe COVID-19 and has therefore prompted the use of cytokine/transduction pathway inhibitors in the treatment of disease. However, numerous markers with different mechanisms of action have been linked to mortality, complicating the understanding of disease pathogenesis and the elaboration of therapeutic strategies.

**Methods:** Retrospective study on COVID-19 hospitalized subjects in the acute phase of disease. A broad range of cytokines (CD25, IL-18, TNF-α, TNF RI, TNF RII, GDF-15, IL-7, LIF, IL-6, CHITINASE3_LIKE1, RAGE and Pentraxin-3) was assessed on plasma samples (Luminex, ELISA) collected upon hospitalization. Subjects were divided into two groups according to their clinical in-hospital death (Survivors: S; Non-Survivors: NS). Comparisons between groups were performed by Fisher's exact test or Mann–Whitney U test as appropriate. The association between each variable and mortality was analysed through univariate and multiple logistic regression models. Subsequently, survival analysis was conducted with Cox proportional hazard models.

**Results:** 77 hospitalised Covid-19 patients were enrolled: 42 S and 35 NS (Figure 1A). As expected, in the NS group we found a higher proportion of subjects with fever and dyspnoea upon admission, development of ARDS and need of PEEP respiratory support (Figure 1A). NS also displayed significantly higher blood neutrophils/lymphocytes, C-reactive protein, LDH and procalcitonin as well as lower PaO2/FiO2 and peripheral O2 saturation values at admission (Figure 1A). In keeping with these findings, CD25, IL-18, IL-6, TNF-α, TNFRI, TNFRII, GDF-15, IL-7, LIF and Chitinase3_Like1, Pentraxin-3 and RAGE were significantly higher in NS than S (Figure 1B) and were associated to mortality in univariate regression models. In the multivariate regression model GDF-15 and fever were the two more relevant features associated with mortality (Figure 1C). In the survival analysis GDF-15 was the strongest predictor of mortality (HR 2,26, 1,55-3,31; p<0,01 reference group bottom quartile Figure 1D, E).

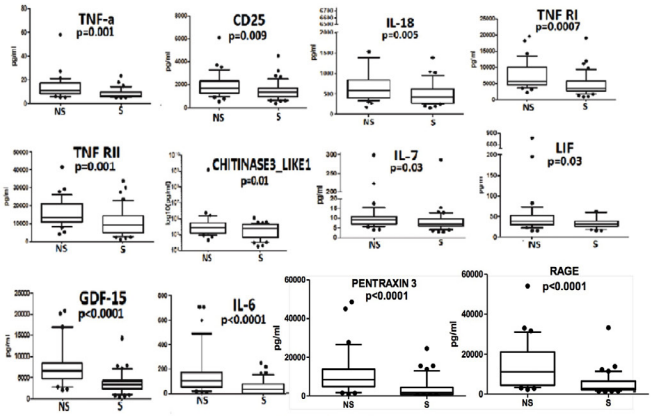
**Conclusion:** Our in-depth characterization of the cytokine storm demonstrates that GDF-15 is an independent predictor of Covid-19 mortality. Given the reported increase of this cytokine with age and its possible mechanistic role in various pathological conditions, our findings suggest that GDF-15 signalling pathway inhibitors may be included as possible therapeutic candidates for Covid-19.

**1A**

| Demographical and clinical characteristics | All patients (N = 77) | Survivors (N = 42) | Non-survivors (N = 35) | p-Value |
|---|---|---|---|---|
| **Sex** | | | | |
| Female | 37 [48%] | 20 [48%] | 17 [49%] | p = 1,0000 |
| **Age, y** | 79 [70-86] | 74 [66-84] | 84 [75-87] | **p = 0,0198** |
| **Comorbidities** | | | | |
| Hypertension | 51 (66) | 29 (69) | 22 (63) | p = 0,6326 |
| Cardio-vascular disease | 38 (49) | 22 (52) | 16 (46) | p = 0,6492 |
| Dementia | 17 (22) | 7 (17) | 10 (29) | p = 0,2728 |
| Chronic pulmonary d. | 9 (12) | 3 (7) | 6 (17) | p = 0,2858 |
| Cancer | 9 (12) | 3 (7) | 6 (17) | p = 0,2585 |
| Chronic kidney disease | 20 (26) | 10 (24) | 10 (29) | p = 0,7947 |
| Diabetes | 25 (32) | 16 (38) | 9 (26) | p = 0,3297 |
| **Age adj. charlson score** | 3 [3-4] | 3 [2-4] | 4 [3-4] | **p = 0,0249** |
| **Symptoms at the admission** | | | | |
| Fever | 53 (69) | 23 (55) | 30 (86) | **p = 0,0060** |
| Cough | 26 (34) | 12 (29) | 14 (40) | p = 0,3385 |
| Dyspnea | 43 (56) | 17 (41) | 26 (74) | **p = 0,0053** |
| Fatigue | 15 (19) | 9 (21) | 6 (17) | p = 0,7750 |
| Diarrhoea | 3 (4) | 1 (2) | 2 (6) | p = 0,5880 |
| **Radiological pulmonary infiltrates** | 67 (87) | 34 (81) | 33 (94) | p = 0,1009 |
| **Need of oxygen-therapy** | 17 (22) | 8 (19) | 9 (26) | p = 0,5844 |
| **Respiratory parameters** | | | | |
| $pO_2$ | 72,1 [62,5-88] | 72,4 [65-85] | 67,2 [61,5-91,5] | p = 0,3964 |
| $pO_2/FiO_2$ | 307 [249-358] | 329 [289-369] | 291 [199-346] | **p = 0,0126** |
| $SpO_2$ | 96 [91-97] | 96 [93-98] | 95 [89-97] | **p = 0,0362** |
| ARDS | 36 (47) | 15 (36) | 21 (60) | **p = 0,0411** |
| **Symptom onset - hospitalization**, days, | 4 [2-8] | 5 [2-9] | 4 [2-7] | p = 0,6378 |
| **Symptom onset - discharge/death**, days | 18 [11-35] | 30 [17-48] | 12 [8-18] | **p = 0,0000** |
| **Admission - discharge/death**, days | 12 [6-25] | 22 [10-38] | 7 [4-14] | **p = 0,0000** |
| **Need for positive end-expiration pressure** | 42 (55) | 28 (67) | 14 (40) | **p = 0,0233** |
| **Blood examinations** | | | | |
| WBC count, $10^3/\mu L$ | 7,00 [5,42-9,71] | 7,25 [6,19-9,59] | 6,43 [4,77-9,69] | p = 0,2353 |
| Neutrophils, $10^3/\mu L$ | 4,93 [3,93-7,51] | 4,93 [4,06-7,50] | 5,15 [3,58-7,69] | p = 0,8419 |
| Lymphocytes, $10^3/\mu L$ | 1,04 [0,64-1,34] | 1,16 [0,69-1,72] | 0,82 [0,62-1,15] | **p = 0,0082** |
| Neutrophils/Lymphocytes ratio | 5,16 [3,12-9,81] | 4,09 [2,78-7,78] | 7,49 [3,97-11,14] | **p = 0,0284** |
| CRP, mg/L | 69 [27-99] | 45 [21-80] | 80 [59-121] | **p = 0,0047** |
| LDH, U/L | 288 [211-390] | 266 [206-348] | 340 [272-442] | **p = 0,0247** |
| Procalcitonin, ng/mL | 0,13 [0,07-1,21] | 0,08 [0,05-0,17] | 0,57 [0,10-5,0] | **p = 0,0038** |
| Creatinin, mg/dL | 1,3 [1,0-2,2] | 1,2 [0,9-1,7] | 1,3 [1,1-2,3] | p = 0,3026 |
| eGFR CDK-EPI formula | 48,4 [26,2-61,3] | 53,2 [33,7-72,9] | 46,1 [26,0-57,8] | p = 0,2670 |

Clinical, demographic and biohumoral characteristics upon admission. Continuous variables expressed as median, IQR. Categorical variables expressed as number, %

1B




Statistical analyses: box-plots represent medians and 10th-90th percentile range. Comparison between groups carried out with Mann-Whitney test.

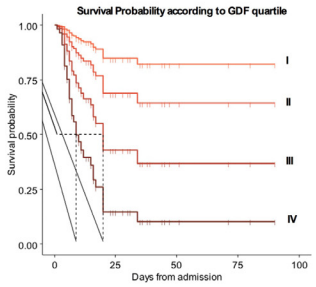
1C

| Multivariate Analysis | | |
|---|---|---|
| Variable | OR (95% CI) | p value |
| Age ≥ 75 y | 4,72 (0,54-51,69) | 0,1747 |
| Age-adjusted CCI | 1,01 (0,31 3,25) | 0,9819 |
| eGFR (by CKD-EPI), ml/min | 1,004 (0,98-1,03) | 0,7832 |
| PCR, mg/L | 1,006 (0,99-1,02) | 0,5009 |
| Fever | 4,84 (0,98-29,44) | **0,0540** |
| Dyspnea | 2,29 (0,58-9,59) | 0,2386 |
| P/F at admission | 0,997 (0,990-1,004) | 0,4244 |
| GDF-15, quartiles | 3,27 (1,77-6,72) | **0,0004** |

1D

| Survival Analysis Using Cox Regression | | |
|---|---|---|
| Variable | OR (95% CI) | p value |
| Age ≥ 75 y | 2,61 (1,11-6,13) | **0,02780** |
| Fever | 3,54 (1,31-9,57) | **0,01270** |
| P/F at admission | 0,996 (0,992-0,999) | **0,01740** |
| GDF-15, quartiles | 2,26 (1,55-3,31) | **0,00002** |

1E




## 207 ANGIOTENSIN II CAUSES T LYMPHOPENIA VIA REACTIVE OXYGEN SPECIES IN SEVERE COVID-19

**Lucy Kundura**[1], Sandrine Gimenez[1], Renaud Cezar[2], Sonia André[3], Yea-Lih Lin[1], Clément Mettling[1], Philippe Pasero[1], Laurent Muller[2], Pierre-Géraud Claret[2], Sandra Duvnjak[2], Paul Loubet[2], Albert Sotto[2], Tu-Anh Tran[2], Jérôme Estaquier[4], Pierre Corbeau[4]

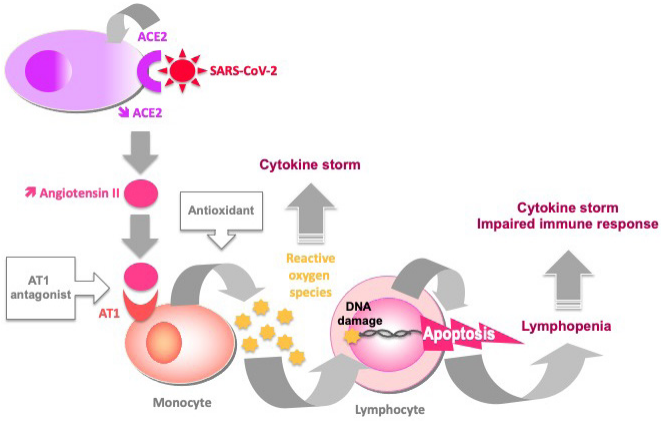
[1]*Institute of Human Genetics, CNRS, Montpellier University, Montpellier, France,* [2]*Nîmes University Hospital, Nîmes, France,* [3]*INSERM-U1124, Université de Paris, Paris, France,* [4]*Montpellier University, Montpellier, France*

**Background:** The aim of this study was to identify the cause of lymphopenia, strongly predictive of survival in COVID-19.

**Methods:** We recruited PCR-positive SARS-CoV-2-infected patients upon admission to Intensive Care Units (ICU, n = 29) and to the Infectious Diseases Department (non-ICU, n = 29) at Nîmes University Hospital, as well as age-and sex-matched healthy controls (HC). Their Angiotensin II plasma levels were measured by ELISA and their monocytic reactive oxygen species (ROS) production and T-cell apoptosis were measured by flow cytometry using dichloro-dihydro-fluorescein diacetate and fluorescent annexin V, respectively. DNA damage and double strand breaks were quantified in immunofluorescence using antibodies specific for -γ-H2AX and 53BP1, respectively.

**Results:** The monocytes of certain COVID-19 patients spontaneously released ROS able to induce DNA damage and apoptosis in neighboring cells. High ROS production was predictive of death. Indeed, in most patients we observed the presence of DNA damage in up to 50% of their peripheral mononuclear blood cells, with double-strand DNA breaks, and T-cell apoptosis. The intensity of this DNA damage was linked to lymphopenia. SARS-CoV-2 is known to induce the internalization of its receptor, Angiotensin Converting Enzyme 2, a protease able to catabolize Angiotensin II. Accordingly, we observed high plasma levels of Angiotensin II in ROS-producing patients. In search of the stimulus responsible for their ability to release ROS, we unveiled that Angiotensin II triggers ROS production by monocytes via Angiotensin receptor I (AT1). ROS released by Angiotensin II-activated monocytes induced DNA damage and apoptosis in neighboring cells.

**Conclusion:** Mononuclear cell apoptosis provoked via DNA damage due to the release of monocytic ROS could play a major role in COVID-19 pathogenesis, inasmuch as ROS are also known to trigger inflammatory cytokine production. Unveiling this new pathogenic pathway opens up new therapeutic possibilities for COVID-19 based on the early association of AT1 antagonists and antioxidants.




## 208 INHIBITION OF HIV-1 INFECTION IN SICKLE CELL DISEASE

**Sergei Nekhai**[1], Namita Kumari[1], Asrar Ahmad[1], Marina Jerebtsova[1], Andrey I. Ivanov[1], Sharmin Diaz[1], James G. Taylor[1]

[1]*Howard University, Washington, DC, USA*

**Background:** We previously demonstrated inhibition of ex vivo HIV-1 infection in PBMCs obtained from patients with Sickle Cell Disease (SCD). We hypothesized that sickle cell hemoglobin (HbS) released by sickled red blood cells leads to the upregulation of innate antiviral response in T cells and macrophages and inhibition of HIV-1 replication. Here, we tested this hypothesis and also analyzed HIV-1 infection in vivo using mouse model of SCD infected with mouse-adapted EcoHIV.

**Methods:** RNA Seq was conducted on total RNA obtained from HbS –treated THP-1 derived macrophages and non-activated and activated PBMCs using Illumina® NextSeq 500.. Townes mouse model of SCD was used in the study and infected with EcoHIV virus that was propagated in 293T cells.

**Results:** RNA Seq analysis of RNA obtained form THP-1 cells differentiated into macrophages with PMA and treated with HbS or HbA showed upregulation of several restriction factors including IFIT3, LGALS3BP, MX2 and RTF1 (1.5-2.3 fold). Ingenuity pathway analysis showed upregulation of IRF-7 signaling pathway and down regulation of viral infection and replication. RNA Seq analysis of non-activated SCD PBMCs compared to control showed upregulation of PKR (15-fold, p=1 x 10-11). Additional restriction genes (1.5-3 fold increase) included APOBEC3B, BST2, CPSF6, IFI16, IFITM3, ISG15, LGALS3BP, PML and RTF1. In activated SCD PBMCs, four genes previously linked to HIV-1 inhibition included APOBEC3A (23-fold, p=2 x 10-5), CH25H (11-fold, p=4 x 10-5), heme oxygenase-1 (HO-1, 13-fold, p=1.5 x 10-12) and ferroportin (FPN, 5-fold, p = 9 x 10-8). Several additional genes (1.5-3-fold increase) includede APOBEC3B, BRD4, CD40, CDKN1A (p21), GDR1, IFIT3, IFITM3 and SAMHD1. We confirmed the expression CH25 and HO-1 and validated their antiviral role in SCD PBMCs using small molecule inhibitors. Finally, analysis of EcoHIV infection in SCD Townes mice showed significant down regulation of HIV-1 gag and nef mRNA levels in the spleen of SCD mice at day 7 post infection compared to control mice. SCD mice also had increased FPN and SAMHD1 expression levels in spleen.

**Conclusion:** We demonstrated that HbS treatment elicits strong antiviral state which is further supported by PKR expression in non-activated SCD PBMCs. Activated SCD PBMCs express many antiviral factors that facilitate robust anti-HIV-1 effect and block viral replication. Suppression of EcoHIV infection in SCD mice further support the idea that HIV-1 infection is suppressed in patients with Sickle Cell Disease.

**209 THE GUT MICROBIOTA IMPACTS SUSCEPTIBILITY TO HIV**

New Investigator Scholar

**Danting Jiang**[1], Ria Goswami[2], Sedem Dankwa[2], Sallie Permar[2], Neeraj K. Surana[1]
[1]*Duke University, Durham, NC, USA,* [2]*Weill Cornell Medicine, New York, NY, USA*

**Background:** The HIV/AIDS epidemic remains one of the world's most critical public health problems. Following decades of research on HIV pathogenesis, there is a growing number of studies that have characterized in HIV-infected patients a dysbiosis of the gut microbiota, the diverse communities of microorganisms that play a fundamental role in host physiology. However, it is still unclear whether the gut microbiota affects susceptibility to HIV infection.
**Methods:** We analyzed a collection of microbiome and immunological data from infant rhesus macaques in a pediatric HIV vaccine study, which includes HIV and control vaccine groups (immunized at 0, 6, and 12 weeks of age; n=12/group). Starting from 15 weeks of age, all monkeys were orally challenged with SHIV every week until they became infected. The microbiome data was generated from 16S rRNA gene sequencing of macaque fecal samples and was processed using the DADA2 pipeline. We utilized microbe-phenotype triangulation, an innovative platform previously developed by the lab, to identify bacterial taxa that are related to HIV susceptibility. We also investigated the Spearman's correlation between the gut microbiota and immune parameters measured from mucosal and blood samples of the study animals.
**Results:** Although the HIV vaccine did not confer protection, the animals exhibited variable time to acquisition of SHIV. We compared the overall bacterial communities in both groups of animals and found that, despite its failure to provide protection, the HIV vaccine induced changes in the gut microbiota. Additionally, we identified 6 bacterial taxa that were bioinformatically associated with increased susceptibility of HIV and 2 taxa that were associated with decreased susceptibility. The relative abundance of these taxa also correlates significantly, in both directions, with immune phenotype parameters that indicate immune activation status. Importantly, one of the protective taxa, Lactobacillus gasseri, has been experimentally confirmed as inhibiting HIV infection of human tissue in vitro, which helps validate our overall findings.
**Conclusion:** Our results demonstrate that the gut microbiota impacts acquisition of HIV, potentially by modulating host immune activation. The causal effect of the bioinformatically identified taxa on HIV infectivity is now being validated in vitro with a cell line model. Our finding adds a new perspective to the existing knowledge of HIV pathogenesis and provides innovative insights on the preventive and therapeutic of HIV.

**210 EFdA OFFERS COMPLETE PROTECTION FROM REPEATED PENILE HIV CHALLENGES**

**Martina Kovarova**[1], Sarah E. Wessel[1], Claire E. Johnson[1], Myron S. Cohen[1], J. Victor Garcia-Martinez[1]
[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** Unprotected heterosexual intercourse is the most common route of HIV transmission. Men comprise approximately half of the HIV-infected population worldwide. Sexually transmitted HIV infections in exclusively heterosexual men are acquired through the penis. Prevention methods for this mode of transmission are condom use and circumcision. However, low adherence to condom use and the fact that 40% of circumcised men are not protected highlight the need for additional more effective prevention strategies. We tested 4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA), a potent NRTTI with low cytotoxicity, for the prevention of penile HIV transmission.
**Methods:** Male genital tract (MGT) of bone marrow/liver/thymus (BLT) humanized mice was evaluated for human cell reconstitution by flow cytometry. Location of human cells in the MGT was assessed by immunohistochemistry and compared to human tissue. HIV infected BLT mice were treated with EFdA orally (1.8 mg/kg) and suppression of the HIV infection in MGT tissues evaluated to confirm EFdA penetration. BLT mice treated with EFdA (n=9) or untreated (n=11) were exposed to multiple doses of transmitted/founder HIVCH040 via the penis. Animals were evaluated for HIV infection for 4 weeks after last HIV exposure (DNA and RNA).
**Results:** MGT of BLT humanized mice including testes, epididymis, seminal vesicles, prostate, and urethra were repopulated with human T and myeloid cells and their location within tissues was comparable to human. The majority of the human T cells in the MGT express CD4 and CCR5 and were susceptible to HIV after intravenous exposure to HIV. Treatment of HIV infected BLT mice with EFdA results in a dramatic reduction (2-3 log) in HIV replication and the restoration of CD4+ T cell levels throughout the entire MGT, demonstrating the efficient penetration of EFdA into the entire MGT. Penile exposures to HIVCH040 resulted in systemic HIV infection in 6 of 11 humanize mice. None of the mice treated with EFdA became infected (p=0.0117).
**Conclusion:** Our data demonstrate efficient suppression of HIV by EFdA in the entire MGT. Pre-exposure prophylaxis with EFdA efficiently prevents penile HIV transmission. These data support further clinical development of EFdA as a potential pre-exposure prophylaxis agent to prevent HIV transmission in men.

**211 VAGINAL PROTEOME ALTERATIONS ASSOCIATED WITH HIV ACQUISITION IN THE VOICE TRIAL**

**Christina Farr Zuend**[1], Samantha Knodel[2], Laura Noël-Romas[2], Sausan Azzam[1], Marlon De Leon[1], Kateryna Kratzer[3], Zvavahera Chirenje[4], Sharon L. Hillier[5], Jeanne Marrazzo[6], Adam D. Burgener[1]
[1]*Case Western Reserve University, Cleveland, OH, USA,* [2]*University of Manitoba, Winnipeg, Canada,* [3]*Dalhousie University, Halifax, Canada,* [4]*University of Zimbabwe Clinical Trials Research Center, Harare, Zimbabwe,* [5]*University of Pittsburgh, Pittsburgh, PA, USA,* [6]*University of Alabama at Birmingham, Birmingham, AL, USA*

**Background:** The mucosal barrier of the female genital tract is the first site for most sexual transmission of HIV and identification of mucosal factors predictive of HIV susceptibility would inform prevention strategies. Here we used unbiased mass spectrometry-based proteomics to characterize vaginal proteins that associate with HIV acquisition in women enrolled in the VOICE (MTN-003) trial.
**Methods:** VOICE was a Phase IIb randomized, placebo-controlled trial to assess HIV pre-exposure prophylaxis with daily oral tenofovir disoproxil fumarate (TDF), oral tenofovir-emtricitabine (TDF-FTC), or 1% tenofovir (TFV) vaginal gel conducted in South Africa, Uganda, and Zimbabwe. Proteomic analysis was performed on vaginal swabs collected at the last HIV seronegative timepoint of women who seroconverted (cases, n=121) and matched swabs from women who remained seronegative (controls, n=381). Differential protein expression was performed using t tests adjusting for multiple comparisons (Benjamini-Hochberg (BH)). IPA software and David Bioinformatics Resource were used for gene ontology and pathway analysis.
**Results:** In this analysis 1,051 human proteins were identified across 502 participants (TDF n=$10_6$, TDF-FTC n=119, TFV n=18, oral placebo n=112, vaginal placebo n=147). Differential protein analysis did not identify any significant differences by study arm (TDF vs Placebo, 6.8%; TDF-FTC vs Placebo, 4.5%; TFV vs Placebo 2.1%, P<0.05). When comparing cases to controls, 284 (27%) proteins were differentially abundant (P<0.05), with 92 passing BH adjustment (32%). These proteins were from pathways related to epithelium development (p=6.8E-3) and innate immune response (p=7.5E-3). PLSDA using 3 proteins selected from LASSO distinguished cases from controls with 68% accuracy (95% CI 64-72%, p=7.9E-10). Cluster analysis grouped women based on expression of these biomarkers (p=5.9E-6) and associated with a 3-fold lower HIV infection risk (OR=3.0, p=5.9E-6). While some biomarkers associated with age or injectable contraceptive use, adjustment for these variables did not impact the relationship with HIV susceptibility.
**Conclusion:** This study identified a high-risk phenotype of reduced mucosal innate immunity and epithelial barrier integrity associated with increased risk of HIV acquisition. Understanding the underlying impact of these biomarkers to mucosal immunity is critical to improve HIV prevention options.
Acknowledgements We thank the VOICE study participants and research team for their support for this study.

**212 VAGINAL MICROBIOME PROFILES IN YOUNG WOMEN AT RISK FOR HIV INFECTION**

**Yiran Wang**[1], Laura Noël-Romas[1], Michelle Perner[2], Samantha Horne[1], Sarah Hoger[2], Kenzie Birse[1], Christina Farr Zuend[1], Lyle R. McKinnon[2], Adam D. Burgener[1]
[1]*Case Western Reserve University, Cleveland, OH, USA,* [2]*University of Manitoba, Winnipeg, Canada*

**Background:** Adolescent girls and young women aged 15-24 in sub-Saharan Africa are disproportionately at risk of HIV infection and are a focus of prevention strategies. Given the known association between vaginal microbial dysbiosis and HIV susceptibility in adult women, we performed an age-stratified analysis of the vaginal microbiome in South African women at risk of HIV acquisition.
**Methods:** Cervicovaginal lavages (CVLs) were collected from participants (n=651) in the CAPRISA 004 microbicide trial and analyzed by mass

spectrometry. Bacterial proteins were identified using the Vaginal Mucosal Proteome database. Participants were grouped by age (18-19 years (y), n=93; 20-24y, n=326; 25-35y, n=232). Proteins were annotated to functional pathways using KEGG Gene Ontology database. Fisher's exact tests and Mann-Whitney U tests were used to compare microbiome types, bacterial taxa, proteins, and functional pathways between age strata, with adjustments for multiple comparisons (Benjamini-Hochberg) while Spearman correlation was used to evaluate across age as a continuous variable.

**Results:** Clinical and epidemiological variables including treatment arm, condom use, cervical ectopy, antibiotic use, and sexual activity were comparable across age groups. Four microbiome types were identified, including: L. crispatus (11.7%), L. iners (44.1%), G. vaginalis (26.1%) or a polymicrobial (15.7%) dominant microbiome. Compared to the 25-35y group, 18-19y and 20-24y women were more likely to have a non-Lactobacillus-dominant microbiome (OR: 1.67, CI: 1.02-2.75, P=0.026; OR: 1.45, CI: 1.03-2.06, P=0.023, respectively), and 18-19y women were also more likely to have a polymicrobial microbiome group (OR: 2.62, CI: 1.00-6.63, P=0.046). The bacterial vaginosis-associated bacteria Megasphaera (r=-0.087, P=0.023) and Atopobium (r=-0.075, P=0.0495) were more common in younger women, as were the inflammatory bacterial pathways of propanoate (r=-0.090, P=0.020) and butanoate metabolism (r=-0.086, P=0.027).

**Conclusion:** In this cross-sectional analysis, younger women were more likely to have a polymicrobial, non-Lactobacillus dominant microbiome, greater abundance of BV-associated bacteria, and expression of bacterial metabolic pathways linked to inflammatory metabolites. These data suggest that differences in the vaginal microbiome may be a contributing factor to increased HIV-1 susceptibility in young women. Acknowledgements: we thank the CAPRISA 004 study participants and research team for their support for this study.

## 213 STROMAL FIBROBLASTS FROM FEMALE GENITAL TRACT DIMINISH THE IN VITRO EFFICACY OF PrEP

New Investigator Scholar

**Ashley F. George**[1], Matthew McGregor[1], Jason Neidleman[1], Warner Greene[1], Nadia Roan[1]
[1]*Gladstone Institutes, San Francisco, CA, USA*

**Background:** Sexual intercourse is the most common means of HIV transmission and worldwide, young women account for the majority of new cases of infections. While pre-exposure prophylaxis (PrEP) has been effective in preventing HIV transmission in MSM, it has proven to be less effective in women. Contributing factors as to why PrEP has been less effective in women include lower adherence due to socioeconomic factors, composition of the vaginal microbiome, and reduced drug concentrations within the female reproductive tract (FRT). Our prior studies have demonstrated that fibroblasts from the lower and upper FRT can markedly enhance HIV infection of CD4+ T cells (by up to 100-fold). Given the current testing of cabotegravir and dapivirine regimens as candidate PrEP agents for women, we set out to determine using in vitro assays whether endometrial stromal fibroblasts (eSF) isolated from the FRT may also affect the anti-HIV activity of these PrEP drugs.

**Methods:** Activated PBMCs from HIV-seronegative individuals were incubated with escalating concentrations of cabotegravir or dapivirine in the absence or presence of eSF. Cells were then infected with an HIV luciferase reporter virus and infection levels were monitored 3 d later by luminescence.

**Results:** Consistent with previous data, eSF enhanced HIV infection rates. The presence of cabotegravir and dapivirine inhibited HIV infection in a dose-dependent manner both in the absence and presence of eSF, but infection rates were on average 3.40-fold higher (range 2.3-4.81) for cabotegravir and 6.06-fold higher (range 2.54-18.44) for dapivirine, in the presence of eSF at a concentration range of 0.012-3.12 nM for cabotegravir and 0.012-4 nM for dapivirine. At high drug concentrations (>3.95 mM), we observe no infection with PBMCs alone, but significant infection rates with eSFs.

**Conclusion:** These data suggest that the antiviral activity of clinically-relevant PrEP drugs are diminished by mucosal fibroblasts abundant in FRT, and suggest that in vitro infection assays testing PrEP using T cells in isolation may overestimate effectiveness relative to what occurs in the FRT. Supplementing PrEP with inhibitors targeting the ability of FRT fibroblasts to enhance HIV infection may increase PrEP efficacy, particularly under limiting drug concentration conditions.

## 214 GERMINAL CENTER B CELLS AUGMENT HIV REPLICATION IN T FOLLICULAR HELPER CELLS

New Investigator Scholar

**Matthew T. Ollerton**[1], Joy Folkvord[1], David Parry[1], Elizabeth Connick[1]
[1]*University of Arizona, Tucson, AZ, USA*

**Background:** T Follicular helper cells (TFH) are highly permissive to HIV and major contributors to HIV replication in untreated and treated individuals. Much work has focused on the role of TFH in generating humoral immunity by activating germinal center B cells (GC B) through expression of the costimulatory molecules CD40L and ICOS. The impact of GC B on HIV replication in TFH, however, has not been assessed. We evaluated the impact of GC B on HIV infection, integration, and expression in TFH using a well-established ex vivo tonsil model of HIV infection.

**Methods:** TFH (CD3+CD8-CXCR5+PD-1hi) and GC B (CD19+CD38+IgD-) were isolated from tonsils of individuals at low risk for HIV infection. TFH were spinoculated with an NL4-3-based GFP reporter virus and cultured with or without GC B in the presence of Saquinavir to prevent spreading infection. Soluble ICOS (sICOS), soluble CD40L (sCD40L), and CD40 antibody were added at 5 µg/ml in a subset of experiments. Percent GFP+ TFH and GFP median fluorescence intensity (MFI) were assessed via flow cytometry after 3 days. DNA was isolated from spinoculated TFH after 18-20 hours in culture. Total and integrated HIV DNA were quantified by qPCR. TFH cell counts were determined using counting beads. Statistical analyses were performed using nonparametric Wilcoxon and Friedman tests and post hoc Dunn's multiple comparison tests.

**Results:** Percent GFP+TFH and GFP MFI were elevated by a median of 52% and 26%, respectively, when cultured with GC B (p=0.001, p=0.0002; n=13). GC B had no impact on total or integrated HIV DNA levels in TFH (p=0.56, p=0.56; n=6) or TFH viability (p>0.99; n=6). Soluble forms of the TFH costimulatory receptors ICOS and CD40L, or CD40 antibody added to GC B and TFH cultures did not affect percent GFP+ TFH and GFP MFI after accounting for differences in the absence of GC B (n=6). GC B did not affect HIV expression when contact between TFH and GC B was minimized by culture in flat-bottom wells, or when physically separated by 0.4 µm permeable membranes (n=8).

**Conclusion:** GC B augment HIV replication in TFH through direct contact. Addition of costimulatory molecules ICOS or CD40L does not further amplify GC B effects on HIV replication in TFH. A better understanding of the mechanisms that underlie GC B-mediated effects on HIV replication could present new targets for suppression of HIV replication in B cell follicles.

## 215 HIV DNA AND ACTIVATION DIFFER FOR LONG-LIVED CD4 CELLS IN LYMPH NODES AND PBMC ON ART

New Investigator Scholar

**Christina Mallarino-Haeger**[1], Maria Pino[1], Elise G. Viox[1], Amélie Pagliuzza[2], Sol del Mar Aldrete[3], Keith A. Delman[1], Michael C. Lowe[1], Nicolas Chomont[4], Vincent Marconi[1], Mirko Paiardini[1]
[1]*Emory University, Atlanta, GA, USA,* [2]*Centre de Recherche du CHUM, Montreal, Canada,* [3]*Medical College of Wisconsin, Wauwatosa, WI, USA,* [4]*Université de Montréal, Montreal, Canada*

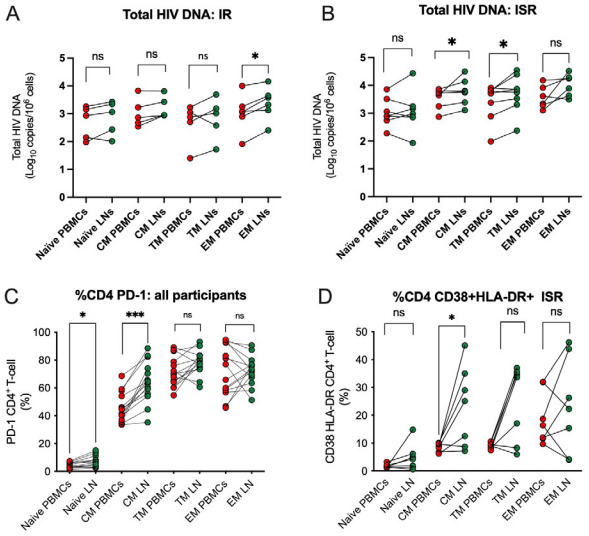
**Background:** Understanding the mechanisms underlying the establishment, persistence, and location of the HIV latent reservoir is a key step for developing cure interventions. T-cell activation and HIV reservoir size are higher in rectal tissue and lymph nodes (LN) compared with peripheral blood mononuclear cells (PBMC). However, the relative contribution of CD4 T cell subsets to this anatomic difference is unknown and it could identify critical targets for an intervention. We sought to identify the relationship between PBMC and LN HIV DNA and activation markers on key T cell subsets: naïve, central memory (CM), transitional memory (TM) and effector memory (EM).

**Methods:** T cell subsets were sorted from 32 people with HIV on ART, including 11 with matched PBMCs and LN, 5 virologically suppressed immunologic responders (IR, CD4 cell count >500 cells/µL <2 years after ART initiation) and 6 virologically suppressed suboptimal responders (ISR, CD4 cell count <500 cells/µL <2 years after ART initiation). We measured HIV DNA, PD-1 and CD38+HLA-DR+expression on T cell subsets.

**Results:** Total HIV DNA was significantly higher in all CD4 T cell subsets from LN compared with those from PBMCs, except for the naïve subset (CM p=0.002; TM p=0.02, EM p=0.002). For subgroups, this difference was significant in CM and TM of ISR while only significant in EM of IR (Figure 1A,B). PD-1 expression was significantly higher in naïve and CM CD4 from LN compared with PBMC (Figure 1C). This difference was maintained in ISR, while IR had significantly higher LN levels of PD1 expression on CM and TM subsets (p=0.016, p=0.047,

respectively). Expression of PD-1 on CD8 T-cells was significantly higher in all subsets derived from LNs as compared to PBMC. Similarly, CD38+HLA-DR+ was significantly higher in CD4 T-cells from LNs compared with those from PBMC in all subsets (naïve p=0.011; CM p=0.005; TM p=0.049) except for EMs and mainly driven by ISR participants (Figure 1D). The same differences were seen in CD38+HLA-DR+ for CD8+ T cells but these were mainly driven by IR participants.

**Conclusion:** HIV-DNA content, T cell immune activation and PD-1 expression, particularly for long-lived CD4 T-cell subsets such as CM and TM, are higher in LN than PBMCs. The differences in those parameters between the two anatomic compartments are further pronounced in or specific for ISR, thus highlighting increased residual disease in LN as a critical feature of and a potential mechanism for individuals with poor CD4 T cell reconstitution during ART.




**Key:**
PBMC: peripheral blood mononuclear cells; LN: Lymph node; CM: central memory; TM: transitional memory; EM: effector memory.
Wilcoxon test was performed for statistical significance.
ns p > 0.05 ; * p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 **** p ≤ 0.0001

## 216 SINGLE-CELL ANALYSIS OF A HUMAN TONSIL EXPLANT HISTOCULTURE MODEL OF HIV-1 INFECTION

New Investigator Scholar

**Connie A. Zhao**[1], Tracey Freeman[1], Nadine Schrode[1], Sanjana Shroff[1], Benjamin Tweel[1], Robert Sebra[1], Kristin Beaumont[1], Talia H. Swartz[1]
[1]*Icahn School of Medicine at Mt Sinai, New York, NY, USA*

**Background:** Human immunodeficiency virus type 1 (HIV-1) infection is associated with increased rates of age-associated non-communicable comorbidities, which have been attributed to a chronic, dysfunctional, hyperactive inflammatory state. Studies of HIV-1 infection in the lymphoid environment have revealed inflammatory signalling distinct from that in the periphery, prompting the need for methods to probe the types of lymphoid cells directly and indirectly impacted by infection as well as the underlying inflammatory signalling pathways. We have developed a human tonsil tissue explant histoculture model of HIV-1 infection in which intact tonsil tissue blocks preserve the full native architecture, cellular repertoire, and milieu of lymphoid tissue, and therefore many of the associated cell-cell interactions and functions.

**Methods:** We used single-cell RNA sequencing in conjunction with differential expression, compositional, and network analyses to examine the effects of HIV-1 infection on the transcriptomes of cells from intact tonsil tissue blocks. Human tonsil explant tissue blocks were infected with HIV-1 NL-CI pseudovirus. The tissue blocks were dissociated into single cell suspensions and single-cell RNA sequencing was performed using the 10X Genomics Chromium platform and the Illumina NovaSeq instrument. The R-based package, Seurat, was used to complete data preprocessing, cell identification and cluster annotation, and downstream analysis such as differential expression and compositional analysis. The Metascape program was used to complete network analysis.

**Results:** Uninfected versus HIV-infected tonsil cell populations shared clusters but were distinct in distribution. HIV infection increased representation of cells in certain CD4+ T, B, CD8+ T, natural killer, monocyte, and dendritic cell clusters relative to control, associated with a distinct gene expression profile. The highest represented pathways in clusters favoured in uninfected samples were characterized by immunomodulation whereas those in HIV-infected samples were characterized by immune system activation.

**Conclusion:** Single-cell analysis of human tonsil explant tissue histoculture can be used to characterize lymphoid cell subsets and responses to HIV-1 infection. This type of analysis allows for the study of key subpopulations and signalling mechanisms involved in HIV-1 replication and the associated inflammatory changes, which are typically not accessible via bulk RNA analysis.

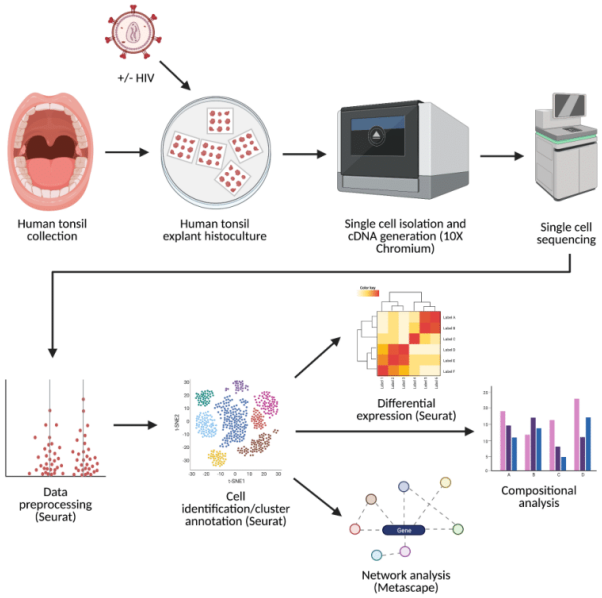



Figure 1. Methods. Created with BioRender.com.

## 217 TEMSAVIR PROTECTS BYSTANDER CELLS FROM ADCC AND BLOCKS CYTOKINE BURST BY MONOCYTES

**Jérémie Prévost**[1], Jonathan Richard[1], Halima Medjahed[1], Romain Gasser[1], Nathalie Brassard[1], Catherine Bourassa[1], Gabrielle Gendron-Lepage[1], Amos Smith III[2], Marzena Pazgier[3], Daniel E. Kaufmann[1], Walther Mothes[4], Andrés Finzi[1]
[1]*Centre de Recherche du CHUM, Montreal, Canada,* [2]*University of Pennsylvania, Philadelphia, PA, USA,* [3]*Uniformed Services University of the Health Sciences, Bethesda, MD, USA,* [4]*Yale University, New Haven, CT, USA*

**Background:** HIV-1 downregulation of CD4 via its Nef and Vpu proteins protect infected cells from antibody-dependent cellular cytotoxicity (ADCC). However, gp120 shed from productively-infected cells can bind CD4 at the surface of uninfected bystander CD4+ T cells, thus sensitizing them to ADCC mediated by CD4-induced antibodies present in the plasma of infected individuals. Soluble gp120-CD4 interaction also induces a cytokine burst by monocytes, including IL-10 secretion. CD4 engages gp120 by introducing its Phe43 in a cavity located at the interface between the inner and outer domains of gp120 known as the Phe43 cavity. The Phe43 cavity residue 375, as well as six co-evolving residues in the gp120 inner domain layers are critical for the stabilization of this cavity. The FDA-approved small molecule temsavir acts as an HIV-1 attachment inhibitor by preventing Env-CD4 interaction. Temsavir binds under the Env β20-β21 loop and in the Phe43 cavity, creating a channel orthogonal to the cavity opening. Here, we evaluated its capacity to prevent ADCC-mediated killing of bystander CD4+ T cells and cytokine burst in monocytes.

**Methods:** The capacity of shed/soluble gp120 to coat uninfected CD4+ T cells and monocytes to sensitize uninfected cells to ADCC and to trigger IL-10 secretion were evaluated by flow cytometry in the presence or the absence of temsavir. These experiments were done with primary blood samples using clade B and CRF01_AE viruses with substitutions within the Phe43 cavity and the gp120 inner domain layers.

**Results:** Temsavir prevents soluble/shed gp120 from interacting with CD4 at the surface of bystander CD4+ T cells and monocytes. This protects bystander CD4+ T cells from ADCC mediated by HIV+ plasma and prevents IL-10 secretion by monocytes. In contrast to clade B viruses, CRF01_AE viruses exhibited natural resistance to the antiviral activities of temsavir. The susceptibility of CRF01_AE viruses to temsavir was restored only when residue 375 and the six co-evolving

inner domain residues were mutated, revealing the critical role of the Phe43 cavity and the inner domain layers in the susceptibility of HIV-1 to temsavir.
**Conclusion:** Our study reveals the capacity of temsavir to protect bystander cells from ADCC and prevents gp120-induced IL-10 production by monocytes, a cytokine with mostly inhibitory activity on immune cells. This suggest that the clinical benefits provided by temsavir treatment could extend beyond blocking viral entry.

## 218 EFFECT OF HIV INFECTION AND ART INITIATION ON GENOME-WIDE DNA METHYLATION

New Investigator Scholar

**Andrés Esteban-Cantos**[1], Javier Rodriguez-Centeno[1], Juan C. Silla[2], Pilar Barruz[1], Fátima Sánchez[2], Gabriel Saiz-Medrano[1], Maria Jimenez-Gonzalez[1], Rosa De Miguel[1], Jose I. Bernardino[1], Rocio Montejano[1], Cédrick Wallet[3], François Raffi[4], Berta Rodes[1], Jose R. Arribas[1]
*[1]Hospital La Paz Institute for Health Research, Madrid, Spain, [2]Spanish National Centre for Cardiovascular Research, Madrid, Spain, [3]University of Bordeaux, INSERM, Bordeaux Population Health Research Center, CHU de Bordeaux, Bordeaux, France, [4]Centre Hospitalier Universitaire de Nantes, Nantes, France*

**Background:** Previous studies provide evidence that HIV infection modulates the host epigenetic landscape with consequences for disease progression. However, there is limited data about the effect of antiretroviral therapy (ART) on epigenetic modifications such as DNA methylation.
**Methods:** We analyzed genome-wide DNA methylation in 44 non-HIV-infected individuals and 184 ART-naïve HIV-infected participants in the NEAT001/ANRS143 clinical trial, before and 96 weeks after ART initiation. DNA from blood samples was bisulfite-converted, and methylation was assessed using the Illumina Infinium MethylationEPIC BeadChip microarray. We compared DNA methylation profiles between HIV-infected and non-infected participants, and the longitudinal changes after ART introduction in the HIV-infected group. Analyses were adjusted by age, sex and DNA methylation-based proportions of leukocyte composition estimated by the Houseman method. We also performed gene ontology (GO) enrichment analyses of the differentially methylated CpG positions (DMP) found among groups.
**Results:** In HIV-infected participants, we observed 7449 DMP between pre-ART and post-ART samples (at significant false discovery rate [FDR] adjusted $p<0.01$). DMP with higher mean differences in methylation after ART initiation ($\Delta\beta>0.1$) were mostly related to genes involved in immune responses and interferon-mediated antimicrobial defenses, such as PARP9/DTX3L, IFI44L and B2M. When we compared HIV-infected participants before starting ART and non-HIV-infected individuals we found 741 DMP, of which 70.4% matched with those that longitudinally changed after ART introduction. In both comparisons, the GO analyses of DMP revealed enrichment in biological processes related to immune system regulation. When comparing HIV-infected participants after 96 weeks of ART (all virologically suppressed) and individuals without HIV, we only found 133 DMP, 76 of which were also differentially methylated before ART. In this case, the analysis of these 133 CpGs that remained differentially methylated after ART showed an enrichment in biological processes related to transcription regulation, DNA damage, cell differentiation and cellular metabolism.
**Conclusion:** The host DNA methylation disruption induced by HIV is mostly restored after two years of successful ART. Further studies are needed to elucidate the biological relevance of the DNA methylation changes that are not restored despite achieving HIV suppression.

## 219 ESTROGEN EXPOSURE MAY ENHANCE TOLL-LIKE RECEPTOR 4 ACTIVATION IN HIV

New Investigator Scholar

**Aaren E. Kettelhut**[1], Emily Bowman[1], Janelle Gabriel[1], Manjusha Kulkarni[1], Jordan Lake[2], Nicholas Funderburg[1]
*[1]The Ohio State University, Columbus, OH, USA, [2]University of Texas at Houston, Houston, TX, USA*

**Background:** Transgender women (TW) are at increased risk for both HIV and cardiovascular disease (CVD). We have reported increased biomarkers associated with CVD in TW regardless of HIV status. Increased bacterial and viral products may drive chronic inflammation in HIV through activation of Toll-like receptors (TLRs). As estrogen can alter TLR expression and function, we hypothesized that exposure of immune cells from cisgender men (CM) with (HIV+) and without (HIV-) HIV to estrogen may enhance TLR activation.
**Methods:** Cryopreserved PBMCs (cryoPBMCs) from HIV- and HIV+ CM, who were unsuppressed (USP) and not receiving anti-retroviral therapy (ART) or suppressed (SP) by ART), (n=10/group) were cultured overnight in the presence of 17-β estradiol or 17-α ethinylestradiol alone or in combination with either TLR4 agonist lipopolysaccharide (LPS) or the TLR8 agonist single-stranded poly-uridine (ssPolyU). Monocyte activation was measured by flow cytometry and cytokine production in supernatants by Legendplex. Plasma immuno-inflammatory biomarkers were measured by ELISA. Statistical analyses included Wilcoxon rank sum, Mann U Whitney, and one-way ANOVA.
**Results:** Median ages in participant groups were similar (median age 49, $p>0.05$). Participants were 43% White, 45% Black, and 12% Asian. CD4 T cell counts were higher in HIV+ ART SP compared to USP participants (793 vs 334 cells/μL, $p<0.001$). Cells from HIV+ CM produced more inflammatory cytokines (TNFα, IL-6) than cells from HIV- CM following exposure to LPS and ssPolyU. Estrogen alone did not activate immune cells from any group but did enhance LPS-induced surface expression of activation markers CD69 and HLADR on monocytes and increased TNFα and IL-6 in cell culture supernatants compared to LPS alone, particularly in HIV+ CM (Fig 1). Similar enhancements with estrogen were not seen with ssPolyU. Plasma markers of immune activation and microbial translocation (eg, sCD14, sCD163, LPS-binding protein) tended to be higher in both HIV+ groups compared to HIV- CMs, with differences in sCD14 and sCD163 reaching significance ($p<0.05$). These markers were positively associated with in vitro responsiveness to estrogen and LPS in HIV+ CM.
**Conclusion:** Persistent immune activation in HIV may prime cells to be more responsive to estrogen and TLR4 ligation. Since HIV-induced immunoinflammatory profiles may contribute to CVD, estrogen therapy in HIV+ TW may exacerbate chronic inflammation, thus increasing CVD risk in this population.

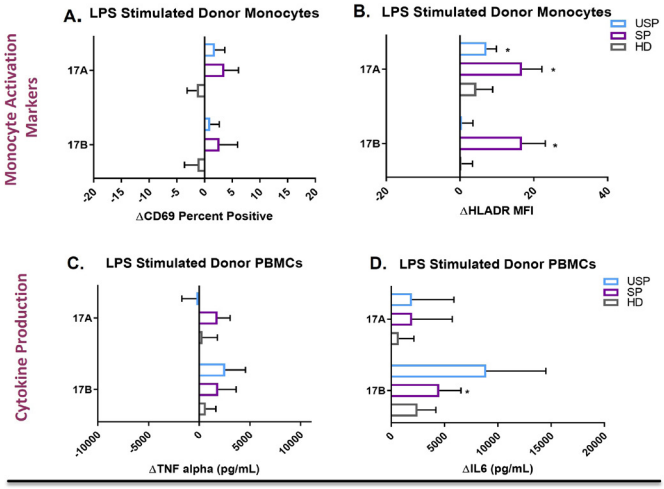



**Figure 1: Immunoinflammatory profiles of HIV+ participants show divergent responses to estrogen in the presence of lipopolysaccharide (LPS) compared to HIV - individuals.** Cryopreserved PBMCs were stimulated overnight with 1uM 17β estradiol (17B) or 17α ethinylestradiol (17A) in the presence of 100ng/mL LPS stimulation in 10% Human AB serum phenol-red free RPMI. Monocyte activation markers (A-B) were measured by flow cytometry after CD14+ monocyte gating (n-=10) and cytokines (C-D) were measured by Legendplex in the supernatants (n=15) of HIV negative (HD), HIV ART-suppressed (SP), and HIV ART-naïve (USP) groups. Data was normalized to LPS stimulation alone. Here we see divergent responses in immunoinflammatory profiles, with greater increases in the HIV+ participants, suggesting potential alterations in TLR4 expression or function. Data is shown as mean and standard error. Statistical analysis shown here is Wilcoxon rank sum. * represents significant differences between LPS stimulation alone vs. LPS with hormones within each group ($p<0.05$).

## 220 EXTENSIVE TRANSCRIPTIONAL PERTURBATIONS IN THE COLON VERSUS BLOOD DURING CHRONIC HIV

**Stephanie Dillon**[1], Kejun Guo[1], Emily Cooper[2], Cheyret Wood[2], Katerina Kechris[2], Mario L. Santiago[1], Cara Wilson[1]
*[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Colorado School of Public Health, Aurora, CO, USA*

**Background:** Chronic HIV-1 infection is known to alter the transcriptional landscape of multiple immune compartments in vivo. However, despite links between alterations in gut homeostasis and comorbid events in people with HIV-1 (PWH), few studies have performed large scale next-generation sequencing analysis of gut tissue to fully evaluate gene regulation in the presence of high HIV-1 viral replication. Moreover, the relative impact of HIV-1 infection on gut versus peripheral blood (PB) transcriptional profiles remains unclear.
**Methods:** Colon biopsies and PB mononuclear cells (PBMC) from 19 untreated, chronically-infected PWH (median HIV-1 RNA/ml: 26000; CD4 T cells/μl: 429) and 13 age, sex-matched uninfected controls, previously collected with informed

consent, were profiled using RNAseq. Differentially expressed genes (DEG) were determined using edgeR (False Discovery Rate (FDR)<0.05 and ≥1.5-fold threshold). Ingenuity Pathway Analysis (IPA) identified canonical pathways enriched in PWH (DEG ≥1.5-fold, FDR<0.05). CD4 T cell frequencies were compared using nonparametric tests.
**Results:** CD4 T cells were significantly depleted in PWH versus controls in colon (2.6x; P<0.0001) and PBMC (1.9x; P=0.03). In colon tissue, 4246 annotated genes were significantly different between PWH and controls with 42.4% expressed ≥1.5-fold higher and 19.7% lower, in PWH. In PBMC 37.3% of all significant DEG (N=831) were upregulated and 34.8% downregulated in PWH versus controls. Only 152 DEG were altered in both compartments. IPA identified 76 activated (z score ≥2) canonical pathways in the colon of PWH, whereas only 7 were identified in PBMC; 4 of these pathways were also activated in the colon. Of note, multiple innate immune cell pathways were activated in colon but not PBMC, including those associated with dendritic cell (DC) and macrophage function (eg, Crosstalk between DC and Natural Killer Cells, Phagocytosis) and inflammatory responses (eg, MIF Regulation of Innate Immunity, TREM1 Signaling, IL-23 Signaling). Few pathways were inhibited in colon (N=3) or PBMC (N=1).
**Conclusion:** Despite declines in CD4 T cells in both colon and PBMC, untreated chronic HIV-1 infection was associated with a more extensive dysregulation of the colon tissue gene expression profile, with heightened expression of multiple pathways. By comparison, PBMC gene transcription signatures were less impacted by HIV-1. These findings further strengthen the case for a role of gut innate immunologic pathways in HIV-1 pathogenesis.

## 221 GUT BARRIER INTEGRITY AND MICROBIOTA IN HIV PATIENTS RECEIVING ORAL BACTERIOTHERAPY

New Investigator Scholar

**Letizia Santinelli**[1], Giacomo Rossi[2], Giorgia Gioacchini[3], Ranieri Verin[4], Giuseppe P. Innocenti[1], Federica Frasca[1], Mirko Scordio[1], Francesca Lombardi[5], Alessandra Piccirilli[5], Stefano Fiorucci[6], Adriana Carino[6], Carolina Scagnolari[1], Giancarlo Ceccarelli[1], Claudio M. Mastroianni[1], Gabriella D'Ettorre[1]
*[1]Sapienza University of Rome, Rome, Italy, [2]University of Camerino, Camerino, Italy, [3]Aalborg University Hospital, Aalborg, Denmark, [4]University of Padova, Padova, Italy, [5]University of L'Aquila, L'Aquila, Italy, [6]University of Perugia, Perugia, Italy*

**Background:** A severe enteropathy with epithelial barrier disruption combined with a chronic T cell immune activation have been reported to characterize HIV-1 immunopathogenesis. Understanding whether the modulation of gut microbiota might promote a reconstitution of intestinal epithelial barrier in HIV-1-infected individuals was the main purpose of the present study.
**Methods:** Gut biopsies and fecal samples were collected from long-term virologically suppressed HIV-1-infected patients (n=10) before (T0) and after 6 months (T6) of high concentration oral bacteriotherapy supplementation (450 × 10^9 billion bacteria, twice a day of Vivomixx®) and from age- and gender-matched healthy controls (n=5). Analysis of fecal microbiota composition was performed by 16S rRNA gene sequencing. The morphology of apical junctional complex and expression of Claudin-2, Occludin, E-cadherin and Zonulin were evaluated in gut biopsies through immunohistochemical assays.
**Results:** HIV-1-infected individuals had a distinct fecal microbiota pattern characterized by a reduction of Bifidobacteriacae (p=0.0290) and Ruminococcaceae (p=0.0280) families compared to uninfected controls. Of note, HIV-1-infected patients receiving oral bacteriotherapy had an increased bacterial biodiversity and richness restoration (Shannon Index: T0 vs. T6, p=0.0182; Simpson Index: T0 vs. T6, p=0.0281), with an abundance of Actinobacteria (T0 vs. T6, p=0.0448) and a decrease of Bacteroidetes levels (T0 vs. T6, p=0.0102). A restoring of intestinal apical junctional complex structure was also observed (T0 vs T6, p<0.0001 for all analysis). Moreover, oral bacteriotherapy resulted in an increase in the levels of Occludin and Zonulin and a decrease in those of Claudin 2 (T0 vs T6, p<0.0001).
**Conclusion:** These findings suggest that six months of oral bacteriotherapy can recover the fecal microbiota alterations and reconstitute intestinal barrier integrity in ART-treated HIV-1-infected patients.

## 222 TNF-A AND IFN-Γ-PRODUCING CD4+ T CELLS MODULATE GUT REGENERATION IN HIV-1 INFECTION

New Investigator Scholar

**Ana Jordan-Paiz**[1], Martin E. Baumdick[1], Johannes Jung[1], Pia Fittje[1], Marcus Altfeld[1], Madeleine Bunders[1]
*[1]Heinrich Pette Institute, Hamburg, Germany*

**Background:** Immune cells in the gastrointestinal tract are critical in host defense against pathogens. Immune cells further contribute to tissue regeneration and can directly interact with intestinal stem cells (ISCs). During HIV-1 infection, mucosal CD4+ T cell populations change dramatically. Early after infection CD4+ T cells infiltrate the intestine, whereas in chronic infection, CD4+ T cells are depleted. How CD4+ T cells affect intestinal stem cells and the repercussions for epithelial regeneration during HIV-1 infection is poorly understood. Here, we mimic acute and chronic HIV-1 enteropathy by using human-derived intestinal organoids (HIOs) in co-culture with HIV-1-infected CD4 T cells.
**Methods:** HIOs were generated by isolating stem cells from healthy intestinal samples. NL4-3 infected and non-infected CD4+ T cells were assessed for cytokine production and used for co-culture at different ratios with ISCs (1:100; 1:10; 1:1; 2.5:1). After 12 days of co-culture, number and size of HIOs were assessed by light microscopy and stem cell marker expression was analyzed.
**Results:** Both infected and uninfected CD4+ T cells produced TNF-α, IFN-γ, IL-17 and IL-22. A ratio of CD4+ T cells to ISCs corresponding to healthy intestines (1:10) resulted in increased number of HIOs compared to cultures without or low (1:100) CD4+ T cells (p<0.0001). Higher numbers of CD4+ T cells (1:1; 2.5:1) as observed in acute infection, reduced both number and size of HIOs (p<0.0001) and severely disrupted the stem cell-ness of the HIOs. HIO growth did not differ upon culture with HIV-1-infected or uninfected CD4+ T cells. To analyze the effect of cytokines on HIO growth, cytokine receptors blockers were used in the co-cultures. Blocking of TNF-α and/or IFN-γ rescued organoid growth upon co-culture with high numbers of CD4+ T cells (1:1; 2.5:1) whereas no effects in growth were observed in co-cultures with the low concentrations of CD4+ T cells.
**Conclusion:** The number of intestinal cytokine-producing CD4+ T cells impact intestinal regeneration. Elevated CD4+ T cell numbers producing higher amounts of TNF-α and IFN-γ, mimicking the situation of acute HIV-1 infection, severely disrupted intestinal development, whereas reduced numbers of CD4+ T cells (chronic infection) resulted in impaired intestinal epithelial regeneration. Taken together, these data demonstrate the impact of intestinal CD4+ T cells on stem cell function and the epithelial barrier during HIV-1 infection.

## 223 HIV-INDUCED CELLULAR SENESCENCE IN PLWH IS DECREASED EX VIVO BY D+Q SENOLYTIC DRUGS

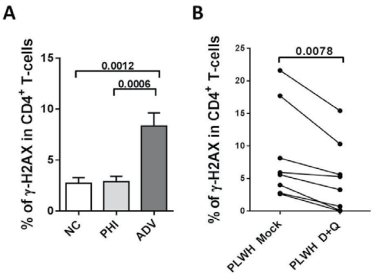
New Investigator Scholar

**Nuria Climent**[1], Víctor Casanova[1], Maria Jose Maleno[1], Andrea Rodríguez-Agustín[1], Sonsoles Sánchez-Palomino[1], Tània González[1], Carmen Hurtado[1], Esteban Martinez[2], Josep Mallolas[2], Juan Ambrosioni[2], Jose M. Miro[3], José Alcamí[1]
*[1]Fundació Clínic per a la Recerca Biomèdica (FCRB), Barcelona, Spain, [2]Hospital Clinic of Barcelona, Barcelona, Spain, [3]Hospital Clinic – IDIBAPS, University of Barcelona, Barcelona, Spain*

**Background:** Despite virologic suppression on ART, PLWH present chronic inflammation and are more vulnerable to age-related diseases and aging. Research in cellular aging has identified key biomarkers that define senescent cells (SC) and new senolytic drugs that can eliminate them. These biomarkers include: SA-βGal, p16INK4a, ϒ-H2AX, IL-6 as a SASP component, Bcl-II and uPAR/CD87. The role of HIV-1 in promoting SC is not fully understood, and could be key in HIV associated aging. We studied SC biomarkers and the effect of ART and senolytics in SC from PLWH with acute (PHI) or advanced (ADV) HIV-infection.
**Methods:** PLWH, from two cohorts with PHI (Fiebig III-VI, VIRECURE) and ADV infection (ADVANZ-4,<100 CD4 cells/µl at diagnosis), before and after a year ART and a group of HIV-negative controls (NC) matched by sex and age were included. Dasatinib plus Quercetin (D+Q) senolytic drugs were added during 3 days to PBMC cultures from those cohorts. SC biomarkers, expression of Gag (KC57), T-cell activation marker CD71 and viability were assessed by flow cytometry on T-cells and monocytes from PBMC's of those 3 cohorts (n=8). Unpaired, paired t-test and Pearson correlations were performed.
**Results:** ADV PLWH had a higher amount of Gag+ and CD71+ T-cells, compared with NC (p=0.0006) and ART was able to reduce this activation. SC markers such as SA-βGal, p16INK4a, ϒ-H2AX (Fig 1A) and Bcl-II were increased in CD4+ (p<0.05) and CD8+ T-cells, especially in ADV vs PHI and NC, and ART do not drop their levels. IL-6 was also higher in CD4+ and CD8+ T-cells from ADV, and in contrast with SC markers, ART normalized these levels (p<0.05). In ADV, a higher proportion of Gag+ and IL-6+ monocytes (M) were observed, whereas CD87+ expression decreased in M. IL-6+ M directly correlate with CD4+ T cells

expressing SC biomarkers such as ϒ-H2AX (p=0.023), p16INK4a (p=0.012) and Bcl-II (p=0.031), but inversely correlated with CD87+-M (r=-0.566 p=0.0004). D+Q senolytic drugs specifically reduced the expression of SC markers as SA-βGal, ϒ-H2AX (Fig 1B, p=0.0078) and IL-6 in CD4+ T cells. This fall was coupled to a rise in cell mortality induced by D+Q.

**Conclusion:** HIV-1 infection raises SC biomarkers in T-cells and increases the amount of IL-6+ monocytes, but reduces CD87 expression in these cells. ART cannot reverse markers of cellular aging excepting IL-6 levels in T cells. Ex vivo D+Q senolytic treatment decreased the levels of SC biomarkers suggesting that these drugs could be useful to reverse cellular senescence in PLWH.




## 224 REDUCED Nef BUT NOT Vpu FUNCTION IN AFRICAN LONG-TERM HIV SURVIVORS VS PROGRESSORS

New Investigator Scholar

**Gisele Umviligihozo**[1], Hua-Shiuan Hsieh[1], Jacklyn K. Mann[2], Steven W. Jin[1], Francis Mwimanzi[1], Hanwei Sudderuddin[3], Zabrina L. Brumme[3], Mark A. Brockman[1]

*[1]Simon Fraser University, Burnaby, Canada, [2]University of KwaZulu-Natal, Durban, South Africa, [3]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada*

**Background:** HIV-1 Nef and Vpu enhance viral pathogenicity through partially overlapping immune evasion functions, and attenuated Nef or Vpu functions have been reported in some individuals with slower disease progression. No studies however have jointly assessed Nef and Vpu functions in the context of slower disease progression. We compared autologous Nef and Vpu functions in 29 long-term survivors (LTS) living with HIV-1 subtype A from Rwanda to those of 62 Vpu and 104 Nef isolates from individuals living with chronic HIV-1 subtype A from the same global region, as controls.

**Methods:** HIV RNA was extracted from plasma, and Nef and Vpu coding regions were amplified by nested RT-PCR. Amplicons were cloned into an expression vector with dual promotors driving Nef or Vpu and GFP expression. The vector used for Vpu cloning additionally featured the HIV-1 Rev Responsive Element (RRE) to enhance expression. After phylogenetic authentication, one Nef and one Vpu clone was analyzed per participant. Clones were transfected by electroporation into an immortalized CD4+ T-cell line (CEM); for Vpu, a plasmid encoding Rev was co-transfected. The ability of each Nef clone to downregulate CD4 and HLA class I (using HLA-A*02 as a representative molecule) and of each Vpu clone to downregulate CD4 and Tetherin was quantified by flow cytometry. The function of each clone was normalized to that of negative (empty vector) and positive (Nef SF2 and Vpu NL4.3) controls.

**Results:** Normalized Vpu-mediated downregulation activity among LTS (median [IQR]) was 0.89 [0.74-1.04] for CD4 and 0.93 [0.78-1.0] for Tetherin, compared to 0.97 [0.83-1.17] and 0.91 [0.84-0.97] in controls; these differences were not statistically significant. In contrast, normalized Nef-mediated downregulation activity among LTS was 0.96 [0.89-0.99] for CD4 and 0.63 [0.39-0.70] for HLA, compared to 0.98 [0.94-1.0] and 0.83 [0.74-0.89] in controls (Mann-Whitney p=0.04 and p<0.0001, respectively). In both LTS and controls, we observed a positive correlation between Nef-mediated CD4 downregulation function and plasma viral load (pVL; spearman r= 0.59, p=0.03 and r=0.30, p=0.005 respectively), but no significant correlations were found between pVL and other protein functions evaluated.

**Conclusion:** Our observation of lower Nef, but not Vpu, functional ability among LTS compared to control participants living with HIV-1 subtype A suggests that Nef impairment may contribute to slower disease progression in African LTS.

## 225 IL-18 AND IL-3 IN EXTRACELLULAR VESICLES: BIOMARKERS FOR A DURABLE ELITE CONTROL

**Eva Poveda**[1], Wendy Fitzgerald[2], Cristina Reglero[1], Manuel Crespo[1], Ana Mariño[3], Hortensia Álvarez[3], Nieves Valcarce[3], Ezequiel Ruiz-Mateos[4], Leonid Margolis[2], Michael M. Lederman[5], Michael L. Freeman[5]

*[1]Galicia Sur Health Research Institute, Vigo, Spain, [2]National Institute of Child Health and Human Development, Bethesda, MD, USA, [3]Hospital Arquitecto Marcide, Ferrol, Spain, [4]Institute of Biomedicine of Seville, Sevilla, Spain, [5]Case Western Reserve University, Cleveland, OH, USA*

**Background:** Elite controllers (EC) with a durable control of HIV-1 replication may represent a model of functional cure. Extracellular vesicles (EVs) have emerged as a mechanism for intercellular communication by targeted delivery of cytokines. We evaluated the cytokine profile associated with EVs in well-characterized cohorts of people living with HIV (PLWH) with different virological control status, including durable and transient EC.

**Methods:** 120 donors were included and divided into 5 groups defined as: 30 antiretroviral therapy (ART)-naïve (median 7 days after HIV diagnosis); 30 ART-treated with nondetectable viremia (median time on ART 9 years); 30 EC who controlled viremia for a median of 14.4 years [15 transient controllers (TC) who ultimately lost virus control, and 15 persistent controllers (PC) who sustained virus suppression], and 30 HIV-uninfected controls. Levels of 39 pro-inflammatory markers in and on EVs isolated by ExoQUIck from stored plasma were quantified using a multiplexed bead-based Luminex assay. Random forest, principal component analysis, and decision trees were performed to identify specific cytokines as a signature of each study group.

**Results:** Overall, the median levels of EV-associated cytokines were 1.33-fold higher among PLWH than for the uninfected control group. Among PLWH, EC showed the highest levels of cytokines (1.11- and 1.32-fold higher compared to ART-exposed and ART-naïve, respectively). Within the EC group, EV cytokine levels were 1.36-fold higher for PC than TC. Higher levels of IL-18 in EVs best distinguished PLWH from uninfected controls (AUC 0.741). In the context of suppressed viremia (EC and ART-exposed), higher levels of IL-18 were associated with EC (AUC 0.942). IL-18 discriminates between EC and ART-exposed with a sensitivity of 73.3% and a specificity of 100%. 96% of participants with suppressed viremia and IL-18 ≥ 2.23 pg/mL were correctly classified as EC. Finally, within EC, higher levels of IL-3 best distinguished PC from TC (AUC 0.824) with a sensitivity of 73.3% and a specificity of 86.7%.

**Conclusion:** EC showed higher levels of EV-associated cytokines compared with other PLWH groups. EV-associated cytokine levels were higher for EC with durable control of HIV-1 replication (PC) than for those without (TC). The role of EV cytokines, intercellular communication and endogenous control of HIV expression should be investigated further.

## 226 SURVIVAL AND DISEASE PROGRESSION IN ART-NAÏVE LTNP WITH UNDETECTABLE HIV-REPLICATION

New Investigator Scholar

**Francisco Diez-Fuertes**[1], Ruben A. Ayala-Suarez[1], Humberto Erick De La Torre-Tarazona[1], José Alcamí[1], Laura Capa[1]

*[1]Institute of Health Carlos III, Madrid, Spain*

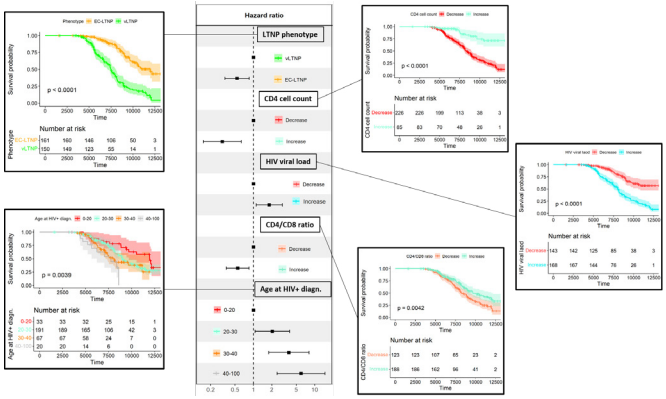
**Background:** A multicenter, prospective study in retrospect including clinical and epidemiological data collected from 21 hospitals and associated with 313 long-term non progressors (LTNP) was carried out

**Methods:** LTNP were ART-naïve HIV-positive individuals who maintained CD4+ T cell counts over 500 cells/µl and viral loads (VL) under 10,000 copies/ml for at least 10 years. Approximately half of participants (52.1%), named elite controllers (EC)-LTNP, were able to maintain undetectable levels of viral replication during at least 10 years. A total of 172 (55.0%) and 42 (13.4%) out of the 313 participants maintained LTNP status for at least 20 and 30 years, respectively. A Kaplan-Meier method and multivariate Cox proportional hazards regression model were used to estimate the probability of survival and progression-free survival for the individuals included in the cohort

**Results:** The study participants were mainly males (64.9%), injecting drug users (IDU; 75.4%), and hepatitis C virus (HCV)-co-infected participants (53%). Different dynamics of changes in clinical parameters during follow-up were found in EC-LTNP compared with viremic LTNP (vLTNP), resulting in lower CD4+ T cell count loss (9.9 versus 24.2 cells/µl/year), higher CD4/CD8 ratio (an increase of 0.01 versus a decrease of 0.09 in ratio) and lesser VL increase (no increase versus 197.2 copies/ml/year). Survival probabilities for all-cause mortality at 30 years from HIV+ diagnosis were 0.90 for EC-LTNP and 0.70 for vLTNP (p=1.9x10-

3). A multivariate analysis revealed that EC-LTNP (HR=0.28; 95% CI: 0.12-0.64) and HCV co-infection (HR=0.40; 95% CI: 0.18-0.91) were associated with improved survival. The probability to preserve LTNP status at 20 years was 0.88 for EC-LTNP and 0.57 for vLTNP, whereas at 30 years, these probabilities dropped to 0.51 for EC-LTNP and 0.18 for vLTNP ($p<10-15$). Risk factors associated to the loss of LTNP status was: higher age at diagnosis and the increase of VL, whereas the increase of CD4+ T cell counts and CD4/CD8 ratio, and the EC-LTNP phenotype were considered protective factors

**Conclusion:** We have identified epidemiological and clinical characteristics differentiating EC-LTNP status from other LTNP with detectable VL, denoting an even better survival and slower disease progression in EC-LTNP. These individuals represent one of the most favorable phenotypes of immune activation against the virus found in nature and, therefore, are strong candidates to be considered as a model of functional cure of HIV-1 infection.




## 227 METABOLIC SHIFTS POTENTIATE ACCELERATED AGING IN SUCCESSFUL LONG-TERM HIV TREATMENT

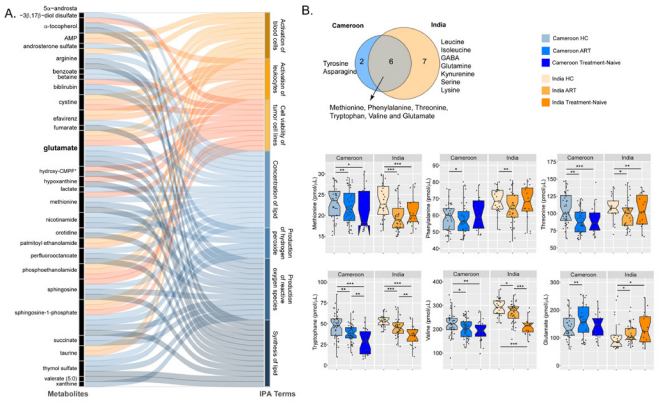
**Flora Mikaeloff**[1], Sara Svensson Akusjärvi[1], George M. Ikomey[2], Soham Gupta[1], Alejandra Escós[1], Luke E. Hanna[3], Kamal Singh[4], Rui Benfeitas[5], Ujjwal Neogi[1]
*[1]Karolinska Institute, Stockholm, Sweden, [2]Maasstad Hospital, Rotterdam, Netherlands, [3]National Institute for Research in Tuberculosis, Chennai, India, [4]University of Missouri, Columbia, MO, USA, [5]Stockholm University, Stockholm, Sweden*

**Background:** Despite successful antiretroviral therapy (ART), persistent low-grade immune activation together with inflammation and toxic antiretroviral drugs can lead to long-lasting metabolic adaptation in people living with HIV (PLWH). The successful short-term cART reported abnormalities in the metabolic reprogramming in PLWH, but the long-term consequences are unknown. The aim of the present study is to investigate alterations in the plasma metabolic profiles by comparing PLWH on long-term cART and matched HIV-negative controls (HC) in two cohorts from low- and middle-income countries (LMIC), Cameroon and India.

**Methods:** Plasma samples were collected from 138 PLWH on cART with more than 5 years), 126 HC, and 45 untreated HIV-infected patients with viremia from Cameroon (n=171) and India (n=138). Untargeted and targeted metabolomics were performed using ultra-high-performance liquid chromatography/mass spectrometry (UHPLC/MS/MS) and LC-MS/MS respectively. Machine learning models were built using R packages Boruta for feature selection, randomForest with 10-fold cross-validation, and python scikit-lean and verified using confusion matrices and the Area under the Receiver Operator Curve.

**Results:** The metabolite set enrichment analysis identified altered amino acid (AA) metabolism and altered oxidative stress [production of reactive oxygen species (ROS) and hydrogen peroxide] as a common factor in PLWH on cART (Fig 1A). Significantly lower levels of neuro-steroids like 5α—androstan—3α,17β—diol monosulfate, androsterone sulfate were observed in both the cohorts. The targeted metabolomics analysis for AA identified six AA that were overlapping between both the cohorts of which five essential AA including methionine, phenylalanine, threonine, valine, and tryptophan were significantly lower (adj $p<0.1$) in PLWH on cART (Fig 1B). Only glutamate was significantly higher in PLWH on cART compared to HC in both cohorts indicating shift in glutaminolysis.

**Conclusion:** In conclusion, our present study based on two cohorts (India and Cameroon) indicated altered AA metabolism and more potentially a switch in glutaminolysis as the alternative pathway for energy production following a long-term antiretroviral therapy. Altered glutaminolysis with long-term treatment and its association with metabolic syndrome, diminished immune recovery, and glutamate excitotoxicity mediated neuro-cognitive impairments can lead to increased co-morbidities and accelerated aging in PLWH with successful therapy from LMICs.




## 228 HIGH-THROUGHPUT TARGETED PLASMA PROTEOMICS SHOWS SYSTEMIC DYSREGULATION IN PWH ON ART

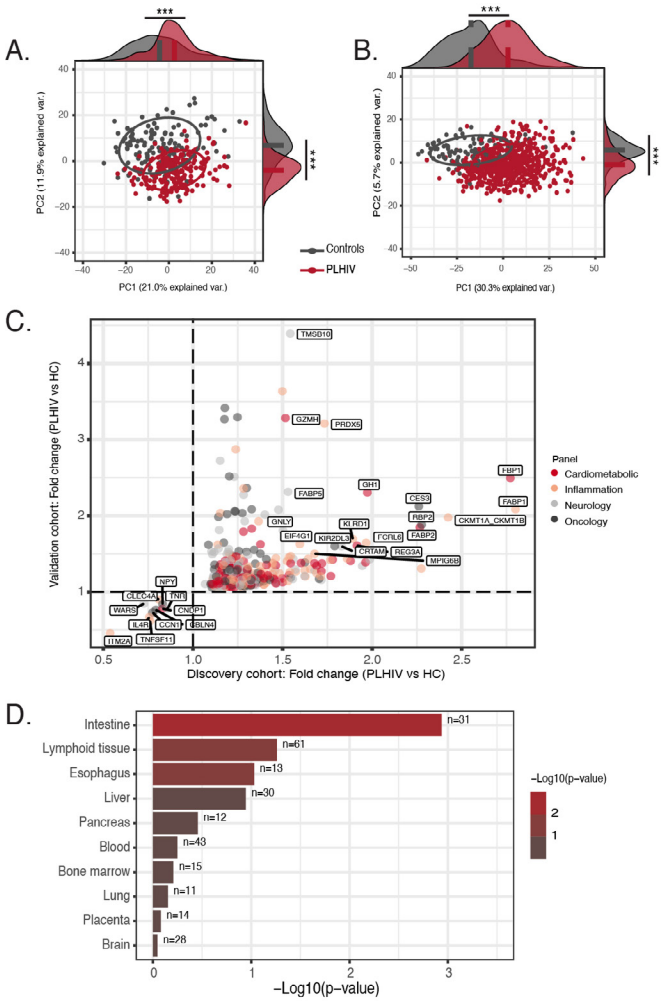
**Nadira Vadaq**[1], Vasiliki Matzaraki[1], Yue Zhang[2], Quirijn De Mast[1], Leo A. Joosten[1], Mihai Netea[1], Jingyuan Fu[2], Andre Van der Ven[1]
*[1]Radboud University Medical Center, Nijmegen, Netherlands, [2]University Medical Center Groningen, Groningen, Netherlands*

**Background:** People with HIV (PWH) in long-term suppressive antiretroviral therapy (ART) are exhibiting increased prevalence of multi-systemic comorbidities compared to the general population. This includes cardiometabolic diseases, HIV-associated neurocognitive disorders, and non-HIV-associated malignancies. Chronic inflammation and microbial dysbiosis are among the major contributors to these major complications in PWH. The main objective of this study is to compare multi-systemic, proteomic profiling between virally suppressed PWH and healthy controls (HC).

**Methods:** This study included a discovery and validation cohort of in total ~900 virally suppressed PWH and ~220 age and sex-matched HC. Proximity extension assay technology is utilized for measurement of 1472 proteins from targeted proteomics platform across four different panels: inflammatory, cardiometabolic, neurology, and oncology. In the discovery cohort of PWH, the absolute concentration of acute-phase protein (hsCRP), microbial translocation marker (IFABP), and monocyte activation markers (sCD14, and sCD163) were measured by ELISA, and shotgun metagenomic sequencing from stool samples was done for identification of gut microbial species.

**Results:** In the discovery and validation cohort, PWH displayed distinct systemic dysregulation of protein expression profile compared to HC (Fig.A and B). Out of 323 differentially expressed proteins (DEP), 313 proteins were upregulated in PWH and equally distributed across the four panels (Fig.C). Among the top proteins (fold-change >1.5) are the fatty acid binding protein group (FABP1 and 2), RBP2, and CES3. Enrichment analysis using publicly available bulk and single-cell transcriptomic data revealed that most of the DEP are originated from the intestine and lymphoid tissue (Fig.D). Pathway analysis of DEP demonstrated lipid and immune-related pathways, with the top pathway of lipid metabolism consisting of the FABP group. In addition, microbiome analysis showed positive influence of microbial species and pathways on DEP originated from enterocytes. Across panels, DEP were markedly associated with increased absolute concentrations of hsCRP, IFABP, sCD14, and sCD163.

**Conclusion:** Targeted proteomic analysis demonstrated a systemic upregulation of protein expression, of which most of the proteins originated from the intestine and lymphoid tissues. These upregulated proteins related significantly to markers of systemic inflammation and IFABP, confirming the known link between gut function and inflammation.




## 229 TARGETED INFLAMMATORY PLASMA PROTEOMICS SHOWS UPREGULATION OF DISTINCT PATHWAYS

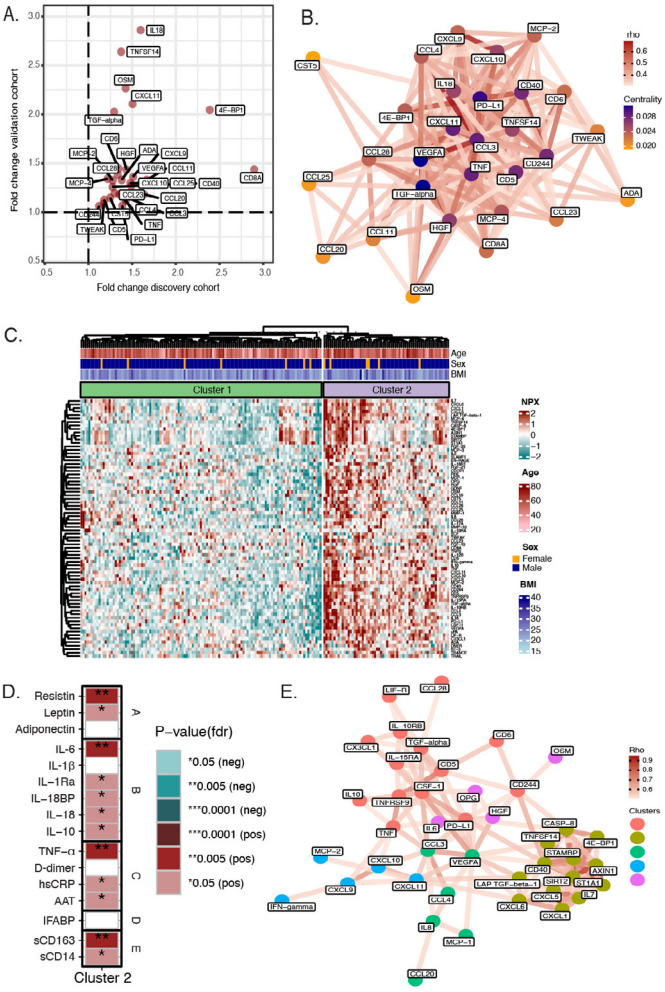
**Nadira Vadaq**[1], Vasiliki Matzaraki[1], Lisa Van de Wijer[1], Louise van Eekeren[1], Leo A. Joosten[1], Mihai Netea[1], Quirijn De Mast[1], Andre van der Ven[1]
*[1]Radboud University Medical Center, Nijmegen, Netherlands*

**Background:** People with HIV (PWH) are exposed to persistent inflammation even using long-term suppressive antiretroviral therapy (ART). Plasma protein profiling may provide a comprehensive unbiassed understanding of the persistent inflammation in PWH using ART.

**Methods:** Targeted proteomic measurements of 92 inflammatory proteins was applied on plasma samples of 192 virally suppressed PWH and 416 healthy controls (HC) using proximity extension assay technology (OLINK proteomics). An independent cohort of 649 virally suppressed PWH and 98 age and sex-matched HC was used to validate the findings. The absolute concentration of 16 plasma inflammatory markers, including hsCRP, TNF-α, IL-6, sCD14, and sCD163 were measured by ELISA. Immunophenotyping and CCR5 expression on immune cells were measured using flow cytometry.

**Results:** PWH had a distinct, increased inflammatory profile compared to HC, both in the discovery and validation cohort (Fig.A). The differentially expressed proteins (DEP) were strongly associated with the absolute concentrations of plasma inflammatory markers. Network analysis of the DEP in PWH revealed that the upregulated proteins belong to mucosal defense chemokines (CCL11, CCL13, CCL20, CCL25, CCL28), CCR5 ligands (CCL3, CCL4), CXCR3 ligands (CXCL9, CXCL10, CXCL11), and growth factors and regulators (TGF-α, HGF, VEGFA, OSM) (Fig.A,B). Unsupervised clustering of plasma inflammatory proteins using the discovery and validation cohort showed two distinct PWH clusters, with one cluster showing a less inflammatory profile (Fig.C). The pro-inflammatory cluster was associated with increased concentrations of plasma inflammatory markers, including TNF-α, IL-6, and sCD163 (Fig.D). Next to DEP found in PWH compared to HC, upregulation of intracellular proteins and CXCR1 and 2 ligands were found in pro-inflammatory cluster (Fig.E). Importantly, some of these DEP (FGF-23, OSM, and HGF) were associated with the presence of cardiovascular diseases in PWH. There was no significant difference of plasma inflammatory proteins between different ART regiments.

**Conclusion:** These findings point towards distinct biological pathways of inflammation in PWH with long-term exposure to ART. This analysis provides new insights on personalized therapeutics interventions in PWH.




## 230 UPREGULATION OF INTERFERON-STIMULATED GENES PERSISTS DURING TREATED HIV-1 INFECTION

**Yunqi Li**[1], Cheryl M. Cameron[2], Banumathi Tamilselvan[2], Manonmani Kumar[2], Brian Richardson[2], Jared Baeten[1], Andrew Mujugira[3], Nelly R. Mugo[4], Connie L. Celum[1], Jairam R. Lingappa[1], Florian Hladik[1], Mark J. Cameron[2], Romel D. Mackelprang[1]
*[1]University of Washington, Seattle, WA, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]Makerere University, Kampala, Uganda, [4]Kenya Medical Research Institute, Nairobi, Kenya*

**Background:** Despite the capacity of antiretroviral therapy (ART) to suppress HIV-1, ART-treated persons living with HIV-1 and undetectable plasma HIV-1 have higher comorbidity rates than people without HIV-1, potentially due in part to chronic immune activation that persists during treatment. We previously found that certain interferon-stimulated genes (ISGs) are persistently upregulated during untreated infection and may contribute to chronic immune activation. Here we hypothesize that ISGs may drive chronic immune activation during suppressive ART use. To evaluate this, we compared ISG expression in peripheral blood mononuclear cells (PBMC) during treated HIV-1 infection to uninfected controls.

**Methods:** We used PBMCs collected from 18 ART-treated individuals with viral suppression and 12 uninfected controls. We used RNA-seq to measure genome-wide gene expression and compared post-ART and uninfected samples using linear models. We used gene-set enrichment analysis (GSEA) of MSigDB's

Hallmark gene sets to determine whether a priori sets of genes in common pathways have similar differences between treated HIV-1 infection and uninfected controls. We accounted for multiple testing using the False Discovery Rate (FDR).

**Results:** Overall, 594 genes were differentially expressed with FDR adjusted p<0.05, of which 254 had an absolute fold-change>1.5. The most significant associations were for CD8A and CD8B, which had ~2.5-fold higher expression in post-ART participants; CD8A and CD8B facilitate cell-cell interactions involving CD8+ T cells. The GSEA found higher expression of genes involved in interferon-α and β responses, including ISGs such as IFI27, CXCL10, OASL, IFI35 and MX1 (adj. p=7.9x10-8 and 1.5x10-13, normalized enrichment scores [NES]=2.3 and 2.4, respectively). Gene sets involved in immune activation, such as TNF-α signaling, inflammatory responses and allograft rejection were also enriched during treated infection (adj. p=1.0x10-8, 1.0x10-4 and 1.6x10-9,

**Conclusion:** We found that genes involved in immune activation, including ISGs and genes involved in CD8+ T cell responses, were enriched in virally suppressed HIV-1 infection compared to uninfected controls. These genes could be targeted to counteract chronic immune activation for an aging population of persons with HIV-1 and long-term ART use. Further study of these ISGs may also elucidate biological mechanisms underlying chronic immune activation during treated HIV-1 infection.

## 231 INFLAMMATION AND IMMUNE ACTIVATION NOT DRIVEN BY ON-ART HIV-SPECIFIC IMMUNE RESPONSES

New Investigator Scholar

**Adam R. Ward**[1], Allison S. Thomas[2], Eva Stevenson[1], Szu-Han Huang[1], Sheila M. Keating[3], Rajesh T. Gandhi[4], Deborah K. McMahon[5], Ronald J. Bosch[6], Bernard J. Macatangay[5], Joshua Cyktor[5], Joseph J. Eron[7], John W. Mellors[5], R. Brad Jones[1]
*[1]Weill Cornell Medicine, New York, NY, USA, [2]Boston University, Boston, MA, USA, [3]GigaGen Inc., San Francisco, CA, USA, [4]Massachusetts General Hospital, Boston, MA, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]Harvard TH Chan School of Public Health, Boston, MA, USA, [7]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** People living with HIV (PLWH) have persistently elevated levels of inflammation and immune activation despite suppressive antiretroviral therapy (ART). Because adaptive immune responses against HIV persist in PLWH on ART, and show evidence of ongoing antigenic stimulation, we hypothesized that they contribute to this phenomenon. We therefore investigated potential associations between HIV-specific T-cell and antibody responses with on-ART inflammation and immune activation.

**Methods:** T-cell responses (IFN-γ ELISPOT) to each HIV gene product as well as to CMV-pp65, and HIV-specific antibody concentrations, were measured in n=101 virally suppressed participants from the AIDS Clinical Trials Group A5321 cohort at study entry (median 7 years on ART). HIV persistence measures including cell-associated (CA)-DNA, CA-RNA, and plasma HIV RNA by integrase single-copy assay (iSCA) were also assessed. Plasma inflammatory biomarkers and T-cell activation and cycling biomarkers were measured at a pre-ART time point and at study entry.

**Results:** Magnitudes of HIV-specific T-cell responses, CMV-pp65-specific responses, and HIV antibody levels were not correlated with levels of inflammatory or immune activation biomarkers, including hs-CRP, IL-6, neopterin, sCD14, sCD163, %CD38+HLA-DR+ CD8+ and CD4+ cells, and %Ki67+ CD8+ and CD4+ cells – including after adjustment for pre-ART biomarker level. Magnitudes of T-cell responses to HIV-Pol were correlated with TNF-α levels, but this was confounded by several factors jointly including pre-ART plasma viral load, CD4+ T-cell count, and CD4+/CD8+ T-cell ratio, years on ART at A5321 entry, and age at A5321 entry. iSCA levels were correlated with CD8+ T-cell activation ($r = 0.25$, $p = 0.027$), but other HIV persistence parameters were not associated with these biomarkers. In statistical mediation analysis, relationships between HIV persistence parameters and inflammatory biomarkers were not mediated or influenced by either HIV-specific T-cell responses or antibody levels.

**Conclusion:** HIV-specific immune responses do not appear to contribute to inflammation and immune activation under long-term ART. These results add to evidence that pre-therapy pathogenic mechanisms are the predominate drivers of long-lasting immune dysregulation and are thus important areas for ongoing research into interventional targets to improve the health of PLWH.

## 232 RECTAL TISSUE HIV RNA IS ASSOCIATED WITH SYSTEMIC INFLAMMATION IN PERSONS WITH HIV

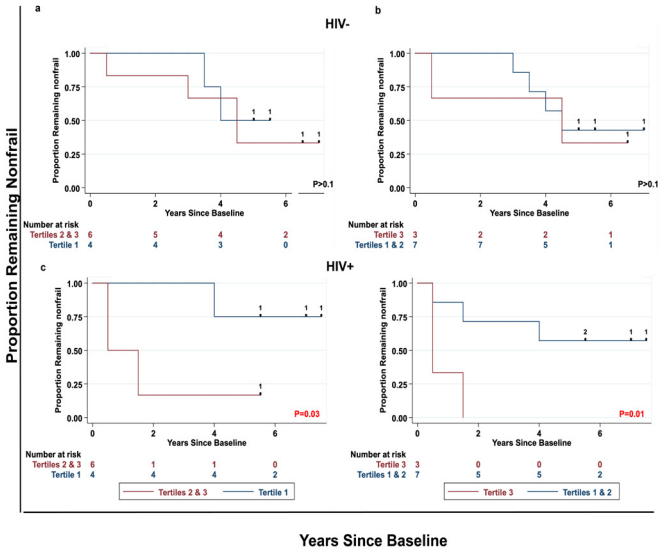
**Cecile D. Lahiri**[1], Kehmia Titanji[1], Monica D. Reece[1], Ruby K. Taylor[1], Renata M. Shaw[1], Shelby Collins[1], Cyra C. Mehta[1], Jessica Ingersoll[2], Igho Ofotokun[1], Susan Pereira Ribeiro[1], Rafick-Pierre Sékaly[1], Christina Gavegnano[1]
*[1]Emory University, Atlanta, GA, USA, [2]Emory Center for AIDS Research, Atlanta, GA, USA*

**Background:** Non-AIDS comorbidities account for significant morbidity/mortality in persons with HIV (PWH). The gastrointestinal tract contributes to systemic immune dysfunction. We assessed associations between detectable rectal tissue (RT) HIV-RNA with 1) systemic inflammatory and hypercoagulation biomarkers and 2) presence of replication-competent virus.

**Methods:** Treatment-naïve PWH initiating dolutegravir-based antiretroviral therapy (ART) underwent blood and RT sampling pre-ART (wk 0) and post-ART (wk 2, 6, 12) between 2/2015 and 9/2019 (NCT 02924389). Plasma and RT HIV-1 RNA was quantitated (Abbott Real-Time HIV-1 Assay; limit <40 c/mL or c/gram). Modified quantitative viral outgrowth assay (QVOA) were performed on a subset of RT samples. Plasma biomarkers (CRP, sCD163, IL-6, TNF-alpha, D-Dimer) were measured by ELISA. Linear regression models were created with each biomarker as the dependent variable and RT suppression status (suppressor vs non-suppressor), biopsy wk (0, 2, 6, 12), and RT suppression status*week as independent variables. Models included random intercept for the participant with a variance components covariance structure.

**Results:** Fourteen participants (71% male; 86% Black, non-Hispanic) contributed 37 paired plasma/RT samples. Median age was 37 years. Absolute CD4 count was 211 cells/$mm_3$. Thirteen of 14 participants achieved plasma virologic suppression at median Wk 6 but only 5/14 achieved RT virologic suppression at any-time-point. Baseline RT HIV RNA and time to plasma virologic suppression were similar for both groups. Modified QVOA was performed on 11 RT samples with detectable HIV RNA; 100% had replication-competent virus. At wk 12, RT suppressors had significantly lower TNF-alpha levels vs non-suppressors: 0.49 pg/mL [95% CI 0.34-72] vs 0.99 pg/mL [0.72-1.37], p=0.008 and lower log D-Dimer levels: 0.91 ng/mL [95% CI 0.27-1.56] vs 1.54 ng/mL [0.91-2.16], p=0.16, Fig 1.

**Conclusion:** Persistent detectable RT HIV RNA and replication-competent virus in the first 12 wks following ART initiation is associated with higher levels of systemic inflammation and hypercoagulation. Early tissue HIV RNA viral dynamics may predict patterns of systemic inflammation and hypercoagulation even during rapid plasma virologic suppression. Larger studies of virally-suppressed patients on long-term ART are needed to confirm findings and assess additional endpoints of subclinical/clinical end-organ disease.



## 233 LONGITUDINAL ASSOCIATION OF SYSTEMIC INFLAMMATION WITH FRAILTY IN HIV-INFECTED MEN

**Weiying Zhang**[1], Jay H. Bream[1], Sean Leng[2], Tricia Nilles[1], Huifen Li[2], Joseph B. Margolick[1]
*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** Chronic HIV infection is associated with chronic inflammation, which may lead to frailty. We previously reported that a) cytomegalovirus (CMV)-specific T cell responses were associated with inflammation, and b) percentages of CD4 T cells producing only IFN-γ in response to CMV (single-producing (SP) cells) predicted onset of frailty positively in HIV- men but negatively in HIV+ men. Here, we explored mechanisms that may account for these different predictions.

**Methods:** 21 men from the Multicenter AIDS Cohort Study (10 HIV-, and 11 virologically suppressed HIV+) who were nonfrail had baseline measurements of serum levels of inflammatory markers (by multiplex electrochemiluminescence) and CMV-specific T cell responses (by intracellular cytokine staining for production of IFN-γ, TNF- and IL-2 in response to overlapping peptide pools spanning 19 CMV open reading frames), followed by semiannual assessments of the Fried frailty phenotype. A series of composite inflammatory scores (CISs) was created by summing the z-scores of log-transformed concentrations of different inflammatory markers. Times to onset of frailty were compared by tertiles of CIS, using Kaplan-Meier estimators and exact log-rank test. Correlations between inflammatory makers and CMV-specific T cells were explored using Spearman's correlation coefficients.

**Results:** A higher CIS with the following formula: CIS= (IL-6+IL-8+Eotaxin-3+MCP-1) – (IL-10+IL-12+IFN-γ+TNF-α+MIP1α+TARC) predicted faster onset of frailty in HIV+ ($p<0.05$), but not in HIV- men over a median follow-up of 6.5 years. Percentages of IFN-γ-SP CD4 T cells were correlated negatively with the composite score in HIV+, but not HIV-, men ($r=-0.73$, $p=.01$ vs $r=0.01$, $p=1$, respectively). In addition, IFN-γ-SP CD4 T cells were significantly less likely to be elicited by CMV glycoproteins in HIV+ men than in HIV- men (median(IQR): 17.6(29.9)% vs 57.1(35.5)%, respectively; $p=.02$).

**Conclusion:** A composite inflammatory score accounting for opposing effects of cytokines/chemokines related to innate immunity and to T cell functions a) predicted onset of frailty in HIV+ men, and b) was negatively correlated with percentages of CMV-specific IFN-γ SP CD4 T cells in HIV+ men only. In addition, the antigenic specificity of these cells suggest that the kinetics of CMV reactivation may differ by HIV status. Together, these results suggest that T cells, especially IFN-γ SP CD4 T cells, may be important in controlling CMV-induced inflammation, and onset of frailty, in HIV+ men.

## 234 ASSOCIATION OF PLASMA BIOMARKERS WITH EARLY MORTALITY IN ADVANCED HIV INFECTION

**Victor Riitho**[1], Roisin Connon[2], Agnes Gwela[3], Josephine Namusanje[4], Ruth Nhema[5], Abraham Siika[6], James Hakim[5], Victor Musiime[4], James A. Berkley[3], Alexander Szubert[2], Nigel Klein[7], A. S. Walker[2], Diana Gibb[2], Andrew J. Prendergast[1]
*[1]Queen Mary University of London, London, UK, [2]Institute of Clinical Trials and Methodology, University College London, London, UK, [3]KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya, [4]Joint Clinical Research Centre, Kampala, Uganda, [5]University of Zimbabwe, Harare, Zimbabwe, [6]Moi University, Eldoret, Kenya, [7]University College London Great Ormond Street Institute of Child Health, London, UK*

**Background:** One-third of people living with HIV in sub-Saharan Africa start treatment with advanced HIV (CD4 count <200/$mm_3$ or WHO stage 3/4 disease), of whom 10% die within three months of initiating ART. We explored the possible contribution of soluble immune and inflammatory markers to early mortality in advanced HIV in Kenya, Uganda and Zimbabwe.

**Methods:** A case-cohort substudy of the REALITY trial (ISRCTN43622374) included 599 patients aged ≥13 years with CD4 <100 cells/$mm_3$ starting first-line ART (2NRTI+NNRTI +/- additional InSTI for 12 weeks). Patients were randomised to standard-of-care prophylaxis (cotrimoxazole) or enhanced prophylaxis [additional isoniazid/pyridoxine (≥12 weeks), fluconazole (12 weeks), azithromycin (5 days) and albendazole (one dose)]. Cases were all deaths ≤24 weeks post-starting ART and controls were a sample of those alive at week 48. Biomarkers were assayed using ELISA and Luminex. Associations of baseline values with all-cause mortality at 24 weeks were analysed using a Cox model (backward elimination, exit $p=0.1$). Similarly, cause-specific mortality was analysed for TB, cryptococcosis, severe bacterial infection (SBI), other and unknown (deaths could be from multiple causes) using Fine & Gray models (death for another cause a competing risk). Models adjusted for prophylaxis randomisation, VL, CD4, WHO stage, age and BMI at enrolment, and centre; and weighted according to inverse probability of selection into the substudy.

**Results:** 169 participants died by 24 weeks (61 TB, 14 cryptococcosis, 21 SBI, 50 other, 70 unknown). Higher CRP, IFNγ, IL-6 and IP-10 were associated with increased risk of all-cause mortality; higher IL-23, IL-2 and RANTES were associated with decreased risk (Table). For cause-specific mortality, higher CRP and sST2 were associated with TB deaths, and higher IL-4 and lower IL-8 with cryptococcosis deaths. SBI deaths increased with higher CRP and lower sCD163. Higher IFNγ and sCD14 and lower IL-9 were associated with other deaths; higher IL-18 and sCD14 and lower TNFα, I-FABP and RANTES were associated with deaths from unknown cause.

**Conclusion:** Soluble inflammatory markers at ART initiation are associated with mortality in advanced HIV in sub-Saharan Africa, with distinct biomarker patterns depending on cause of death. Inflammatory biomarkers (CRP, IFNγ, IL-5 and IP-10) were associated with increased all-cause mortality, while homeostatic and adaptive markers (IL-2, IL-23 and RANTES) were associated with reduced mortality.

| | All-cause | TB | Cryptococcosis | SBI | Other deaths | Unknown |
|---|---|---|---|---|---|---|
| Risk Factors | Hazard ratio | Subhazard Ratio | | | | |
| | per log10 increase (95% CI), p values, * <0.05, ** <0.01, [2] log2 increase | | | | | |
| IL-2 | 0.20 (0.06-0.67)** | | | | | |
| RANTES | 0.32 (0.17-0.60)** | | | | | 0.42 (0.20-0.86)* |
| IL-23 | 0.50 (0.32-0.80)** | | | | | |
| CRP | 1.98 (1.51-2.59)** | 2.01 (1.20-3.39)** | | 2.20 (1.10-4.37)* | | |
| IP-10 | 2.29 (1.39-3.75)** | | | | | |
| IL-6 | 2.84 (1.00-8.06)* | | | | | |
| IFNγ | 3.09 (1.55-6.16)** | | | | 5.90 (1.97-17.66)** | |
| sST2 | | 1.59 (1.09-2.31)*,[2] | | | | |
| IL-8 | | | 0.23 (0.06-0.95)* | | | |
| IL-4 | | | 8.28 (1.90-36.06)** | | | |
| sCD163 | | | | 0.79 (0.63-0.98)*,[2] | | |
| IL-9 | | | | | 0.29 (0.16-0.52)** | |
| TNFα | | | | | | 0.32 (0.12-0.90)* |
| sCD14 | | | | | 1.98 (1.17-3.34)* | 1.81 (1.22-2.70)**,[2] |
| I-FABP | | | | | | 0.76 (0.61-0.95)*,[2] |
| IL-18 | | | | | | 4.51 (1.57-12.97)** |

## 235 STRUCTURAL CHARACTERIZATION OF DNA-ENCODED HIV VACCINES INDUCED NEUTRALIZING ANTIBODY

Late Breaking

**Ziyang Xu**[1], Susanne Walker[2], Megan C. Wise[3], Neethu Chokkalingam[2], Mansi Purwar[2], Alan Moore[4], Jesper Pallesen[4], Daniel W. Kulp[2], David Weiner[2]
*[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Wistar Institute, Philadelphia, PA, USA, [3]Inovio Pharmaceuticals, Inc, Plymouth Meeting, PA, USA, [4]Indiana University, Bloomington, IN, USA*

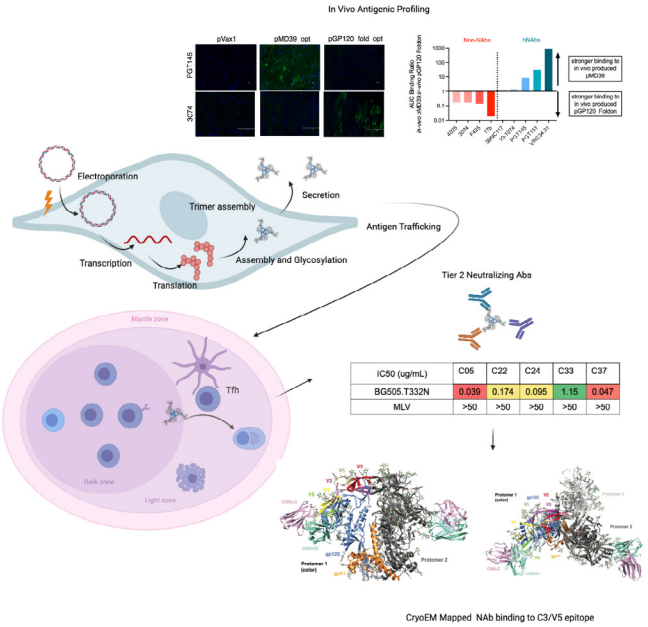
**Background:** Rapid and large-scale deployment of COVID-19 mRNA vaccines highlights the potential utility of developing nucleic acid vaccines (such as RNA and DNA vaccines) against infectious diseases, including HIV-1. However, as compared to SARS-CoV-2, HIV-1 pose some unique challenges- induction of neutralizing antibodies (NAbs) against HIV-1 (frequently a correlate of protection) requires presentation of trimeric and highly conformational epitopes to the immune system, and whether nucleic acid vaccines can enable direct in vivo production of antigens that retain critical antigenic profile has not yet been elucidated. Additionally, it was previously reported that Tier 2 NAbs cannot be induced in mice due to a lack of antibody repertoire, and vaccine studies were suggested to be performed in larger mammals such as rabbits/NHPs, inadvertently slowing down and increasing the costs of preclinical HIV-1 vaccine studies.

**Methods:** In our study, we used the Antigen Conformation Tracing In Vivo by ELISA (ACTIVE) assay developed in house to characterize antigenic profiles of vaccines produced in vivo (from transfected muscle tissues). We analyzed induced cellular responses, using stimulation with overlapping peptides followed by intracellular cytokine staining and IFN-g ELIspot assays. We analyzed induced humoral responses by using both binding ELISA assays and TZM-BL based neutralizing assays, and attempted to map induced NAb epitopes by engineering selectively mutated pseudovirus. We performed antigen-specific B-cell sorting, and used the 10x genomics pipeline to characterize antibody sequences of proliferating B-cell clones.

**Results:** We confirmed that in vivo produced vaccines retained key trimeric conformational epitopes and glycan profiles. Compared to protein vaccination,

DNA vaccination uniquely and strongly induced both TFH, CD4+, CD8+ T-cell responses, and Tier 2 NAbs mapped to a previously unreported Env C3/V5 epitope. 5 unique NAbs were isolated, and confirmed to bind to the epitope using a Cryo-EM structure of NAb-MD39 complex at 3.8Å resolution.

**Conclusion:** Our study confirmed that with appropriate vaccine delivery technology, murine models can be appropriately used for HIV-1 vaccine studies aimed at generating NAb responses. In addition, beyond potential functional immunity gains, DNA vaccines permit in vivo folding of structured antigens and provide significant cost and speed advantages for enabling rapid evaluation of new HIV vaccines.




CryoEM Mapped NAb binding to C3/V5 epitope

## 236 HIV VACCINE CANDIDATE EFFICACY MEDIATED BY CAMP-DEPENDENT EFFEROCYTOSIS AND V2-ADCC

New Investigator Scholar

**Massimiliano Bissa**[1], Sohyoung Kim[1], Veronica Galli[1], Slim Fourati[2], Isabela Silva de Castro[1], Saori I. Fujiwara[1], Mohammad Arif Rahman[1], Guido Ferrari[3], Alexei V. Lobanov[1], George W. Nelson[1], Margaret C. Cam[1], Leonid Margolis[1], Rafick-Pierre Sékaly[2], Gordon L. Hager[1], Genoveffa Franchini[1]
*[1]National Institutes of Health, Bethesda, MD, USA, [2]Emory University, Atlanta, GA, USA, [3]Duke University, Durham, NC, USA*

**Background:** The DNA/ALVAC-SIV/gp120 vaccine significantly decreased the risk of SIVmac251 rectal acquisition. The levels of CD14+ monocytes and the Antibody-dependent cellular cytotoxicity (ADCC) to the V2 of SIV were correlated with reduced risk of acquisition, indicating the central role of innate response in mounting an effective response to vaccination. In-depth understanding of the innate and adaptive responses to vaccination and their cross-talk will elucidate mechanisms of protection and will allow to increase vaccine efficacy.

**Methods:** We integrated different analyses conducted in three separate macaque studies to elucidate how the innate and adaptive responses cooperate in reducing the risk of SIVmac251 acquisition. Animals were immunized with the DNA/ALVAC-SIV/gp120 based-vaccines and vaginally exposed to SIVmac251 either early or late following the vaccination. Analyses of samples collected from vaccinated macaques included canonical assays (ADCC, cell analysis by flowcytometry, luminex and CD14+ efferocytosis of apoptotic neutrophils) together with multiomics (RNA-, microRNA- and ATAC-sequencing).

**Results:** The analyses confirmed the V2-specific ADCC as correlate of reduced risk of viral acquisition. They also identified the efferocytosis mediated by CD14+ cells, a cyclic AMP (cAMP)-dependent engulfment of apoptotic cells, as a new correlate, and its complementation with the V2-ADCC. The study of the transcriptome and the epigenetic landscape of CD14+ cells collected following vaccination showed that durable epigenetic reprogramming of the cyclic AMP/CREB pathway reduces the risk of SIVmac251 acquisition. The importance of cyclic AMP (cAMP)/cAMP response element-binding protein (CREB) pathway activation was further supported by the miR-139-5p, a negative regulator of expression of the cAMP-specific phosphodiesterase PDE4D. Mir-139-5p levels in plasma extracellular vesicles increased following vaccination and correlated with the risk of viral acquisition.

**Conclusion:** Our data posit that, following vaccination, the combination of V2-ADCC and CREB1-mediated efferocytosis, through the prompt and effective removal of apoptotic SIV infected cells, contributes to vaccine efficacy by decreasing inflammation and maintaining tissue homeostasis.

## 237 IMMUNOGENICITY AND PROPHYLACTIC EFFICACY OF ARENAVIRUS-BASED SIV VACCINE IN MACAQUES

**Archana V. Boopathy**[1], Bhawna Sharma[1], Daniela Deutschmann[2], Hoa Truong[1], Johnny Lee[1], Jeffrey Murry[1], Christian Callebaut[1], Romas Geleziunas[1], Wade Blair[1], Klaus Orlinger[2], Sarah Schmidt[2], Henning Lauterbach[2], Tariro Makadzange[1], Sarah Ahmadi-Erber[2]
*[1]Gilead Sciences, Inc, Foster City, CA, USA, [2]Hookipa Biotech, New York, NY, USA*

**Background:** HIV infected elite controllers are characterized by strong HIV specific T cell responses. Likewise, in non-human primate models of SIV infection, SIV-specific CD8 T cell responses have been associated with viral control. These data suggest that CD8 T cells are a key component of an effective immune response to HIV and SIV. Here, we evaluate a novel heterologous arenavirus-based viral vector platform, for immunogenicity and prophylactic vaccination in SIV infection rhesus model.

**Methods:** Healthy rhesus macaques were immunized with replicating arenavirus based vectors, artPICV (artificial Pichinde Virus) and artLCMV (artificial Lymphocytic choriomeningitis virus) in alternating sequence, Ad5/MVA vectors or placebo (Table 1). All viral vectors encoded identical SIVsmE543 gag, env, and pol immunogens. Vaccine immunogenicity was assessed by SIV-specific IFNγ ELISpot and using 51 SIV peptide sub-pools to determine cellular breadth. SIV-specific T cell polyfunctionality, env-specific binding and neutralizing antibodies (nAb), and vector-specific nAbs were also evaluated. Efficacy was determined based on SIV viral load (VL) reduction over 40 weeks post IV challenge with high dose SIVmac251.

**Results:** Vaccination with artPICV/artLCMV or Ad/MVA resulted in significant induction of SIV-specific T cell responses and expansion of immune breadth post 3rd vaccine dose. Both platforms induced SIV specific CD4 and CD8 T cells expressing IFNγ, TNFα, IL2, MIP1β and CD107a. CD8 polyfunctionality was significantly higher after 2nd dose in artPICV/artLCMV than Ad/MVA ($p<0.01$) and after 3rd dose in Ad/MVA than artPICV/artLCMV ($p<0.05$). SIV-specific T cell responses were not impacted by generation of arenavirus vector-specific nAbs. Significantly higher tier 1 nAb to SIVsmE660 were detected post artPICV/artLCMV vaccination compared to Ad/MVA ($p<0.05$). Peak VL was significantly lower in artPICV/artLCMV ($p < 0.05$) and Ad/MVA ($p < 0.05$) than the placebo with ≥1.2 $\log_{10}$ reduction in setpoint VL. No significant difference was observed between artPICV/artLCMV and Ad/MVA for peak or setpoint VL. Gag breadth post 3rd vaccine dose, presence of gag-specific IFNγ-TNFα+IL2+MIP1β +CD107a+ CD8 T cells post LCMV boost and tier 1 SIVsmE660 nAb in artPICV/artLCMV group correlated with lower peak VL (all $p<0.05$).

**Conclusion:** Alternating immunization with arenavirus vectors induces robust SIV-specific T and B cell responses that are not impacted by vector-specific nAbs and reduce VL post SIV IV challenge.

Table 1

| | artPICV/artLCMV | Ad/MVA | Placebo |
|---|---|---|---|
| n/group | 24 | 8 | 8 |
| Immunogen | SIVsmE543 Gag, Env, Pol | | - |
| Vaccine Dose | artPICV: 1x10^6 RCV<br>artLCMV: 4x10^6 RCV | Ad5: 5x10^10 VP<br>MVA: 1x10^8 PFU | - |
| Dosing frequency via IM route | artPICV on week 0 and 20;<br>artLCMV on week 12 and 28 | Ad5 on week 0 and 12; MVA on week 20 and 28 | Buffer on weeks 0,12,20 and 28 |
| SIV challenge | SIVmac251 (28AID$_{50}$; IV route) | | |

## 238 SAMT-247 SYNERGIZES WITH ALVAC-BASED VACCINE TO PROTECT AGAINST SIVmac251 ACQUISITION

New Investigator Scholar

**Mohammad Arif Rahman**[1], Sabrina Helmold Hait[1], Isabela Silva de Castro[1], James D. Stamos[1], Ruth Hunegnaw[1], Melvin N. Doster[1], Tanya Hoang[1], Lisa M. Jenkins[1], David Venzon[1], Manjula Gunawardana[2], Marc Baum[2], Ettore Appella[1], Daniel H. Appella[1], Marjorie Robert-Guroff[1], Genoveffa Franchini[1]
*[1]National Institutes of Health, Bethesda, MD, USA, [2]Oak Crest Institute of Science, Monrovia, CA, USA*

**Background:** The HIV epidemic remains unabated in sub-Saharan Africa, particularly in adolescent women who have limited access to antiretroviral therapy. The deletion of the Env V1 region of the DNA/ALVAC/gp120 vaccine regimen has improved vaccine efficacy and the antiretroviral agent SAMT-247

formulated as vaginal gel has been shown to have an antiviral effect. Here, we tested the hypothesis that the SAMT-247 microbicide targeting the HIV/SIV nucleocapsid protein in combination with DNA/ALVAC/gp120ΔV1vaccination would provide benefit and augment protection against SIVmac251 vaginal challenge.
**Methods:** Thirty-eight macaques were vaccinated with the ΔV1 DNA/ALVAC/gp120/alum vaccines and 12 animals remained naïve. All animals received up to 14 consecutive weekly intravaginal SIVmac251 challenges in the presence (20 vaccinated & 6 naïve) of 0.8% SAMT-247 in HEC gel, or HEC gel only (18 vaccinated & 6 naïve) dosed vaginally 4 hours before each challenge until infection was confirmed. Immunological assays such as ADCC, efferocytosis, ELISA, flowcytometry to measure cell frequencies and cytokine production, with an emphasis on immune responses correlating with vaccine efficacy.
**Results:** The combination of DNA/ALVAC/gp120 vaccination with topically administered SAMT-247 microbicide reduced the risk of SIVmac251 vaginal acquisition by 92.7%, with 80% of macaques remaining uninfected following 14 weekly exposures to the highly pathogenic SIVmac251 strain. Surprisingly, protection by the vaccine-microbicide combination approach exceeded the SAMT-247 (only) antiviral effect suggesting an off-target effect of this small molecule. In vitro experiments using cells from vaccinated animals demonstrated the ability of SAMT-247 to augment NK killing and CD14+ cells mediated efferocytosis, both responses correlating with a reduced risk of virus acquisition in vaccinated animals.
**Conclusion:** These data raise the hypothesis that the SAMT-247 microbicide alters the acetylation state of proteins, leading to displacement of zinc from targets involved in enhancement of the vaccine response. Ongoing experiments will assess if such targets play a role in the microbicide's ability to augment vaccine-induced protection. SAMT-247 is safe and does not induce mucosal inflammation, suggesting that delivery methods aimed to maintain effective drug concentrations in the vaginal mucosa, such as a controlled release intravaginal ring, combined with the DNA/ALVAC/gp120/alum vaccine regimen, may result in durable protection against HIV.

## 239 IL-7 AND IL-15 IMPROVE HUMORAL RESPONSES OF A SHIV DNA VACCINE IN ANIMAL MODELS

**Laury Anne Leroy**[1], Alice Mac Donald[1], Aditi Kandlur[1], Deepanwita Bose[2], Peng Xiao[2], Jean Gagnon[1], François Villinger[2], Yahia Cheboune[1]
*[1]University Grenoble Alpes, St Martin d'hères, France, [2]University of Louisiana at Lafayette, Lafayette, LA, USA*

**Background:** HIV-1 remains a major public health problem all over the world despite efficacious antiviral therapies, but in absence of a vaccine. We developed an innovative lentiDNA vaccine based on the backbone of SHIV-KU2, lacking the integrase gene. In our earlier studies we demonstrated persistent Gag- and Nef-specific CD4+ and CD8+ T precursors (PHPC), central memory (Tcm) and effector memory (Tem) cells up to 80 weeks post-immunization in Cynomolgus macaques. To evaluate whether these memory pools of cells can be amplified, a cassette containing IL-7 or IL-15 gene was inserted into the lentiDNA. Humoral and cellular responses elicited by the two co-injected lentiDNA-IL-7 and lentiDNA-IL15 were compared with those elicited by the parental lentiDNA.
**Methods:** BALB/c mice and Rhesus macaques were immunized by intradermal route with electroporation and intramuscularly with 100 µg (mice) and 5 mg (macaques) plasmid DNA respectively. Mice and macaques received homologous boosts at 6 and 16 weeks post-immunization, respectively. IFN-γ ELISPOT was evaluated on mouse splenocytes and macaques PBMCs and cells of draining lymph nodes respectively. Vaccine specific antibody responses and their functions were examined in serum and rectal secretions. Median values were used for each group, and statistical analyses were done by using unpaired T-test.
**Results:** We found that co-administered lentiDNA-IL-7 and lentiDNA-IL-15 elicited potent Gag- and Nef-specific CD4+ and CD8+ T cells in mice and macaques. The follow-up up to 40 weeks in macaques highlighted the long-term response capacity. Also, Gag-specific Tcm and Tem secreting Granzyme B and MIP-1β were enhanced. Furthermore, non-neutralizing plasma IgG antibodies with ADCC function as well as strong mucosal IgA responses were detected up to 40 weeks post-immunization and enhanced by the adjuvant cytokines in macaques.
**Conclusion:** In summary, co-expression of IL-7 and IL-15 with antigens of our lentiDNA vaccine resulted in augmented proportion and longevity of vaccine-specific CD4+ and CD8+ memory T cells in mouse spleen cells and macaque PBMCs. Concomitantly it also elicited long-lasting responses of plasma IgG together with mucosal IgA and IgG in rectal secretions.

## 240 PROTECTION FROM A PATHOGENIC HETEROLOGOUS SIV BY ELITE CONTROLLERS OF SIVmac239ΔGY

**Pyone Aye**[1], Faith Schiro[1], Amitinder Kaur[1], Marissa D. Fahlberg[1], Lara A. Doyle-Meyers[1], Ronald S. Veazey[1], Christine M. Fennessey[2], Brandon Keele[2], Jeffrey D. Lifson[2], Khader Ghneim[3], Rafick-Pierre Sékaly[3], Michael Gale[4], Mark Marsh[5], James Hoxie[6], Nicholas Maness[1]
*[1]Tulane National Primate Research Center, Covington, LA, USA, [2]AIDS and Cancer Virus Program, Frederick, MD, USA, [3]Emory University, Atlanta, GA, USA, [4]University of Washington, Seattle, WA, USA, [5]University College London, London, UK, [6]Hospital of the University of Pennsylvania, Philadelphia, PA, USA*

**Background:** Correlates of protection from diverse viral strains are sorely needed to inform rational HIV vaccine design. To address this, we are using a nonhuman primate model in which pigtail macaques (PTM) are infected with SIVmac239 harboring a two amino acid deletion in the Env cytoplasmic domain that ablates a highly conserved trafficking signal, leading to elite viral control in nearly all animals in the absence of neutralizing antibodies. We hypothesized that infection with this virus (termed ΔGY) would induce immunity capable of protection from challenge with heterologous SIVsmE660, which is highly pathogenic in PTM, enabling the identification of effective immune responses that may be recapitulated in future vaccines.
**Methods:** Cohorts of ΔGY-controlling PTM were challenged i.v. with SIVsmE660 at various time points after ΔGY infection ranging from ~30 weeks (short-term, n=2) to >5 years (long-term, n=6). Naïve control PTM (n=5) were also challenged. Plasma viral loads were followed using an assay capable of discriminating between SIVmacΔGY and SIVsmE660 RNA. Innate and virus-specific adaptive cellular responses in blood and gastrointestinal sites were tracked over time before and after SIVsmE660 challenge to identify correlates.
**Results:** We found that acute ΔGY infection induced robust antiviral CD8 and CD4 responses detectable in both blood and gastrointestinal tissues that were maintained during ΔGY control. ΔGY-controlling PTM challenged with SIVsmE660 at 5.1, 5.4 and 9.2 years after ΔGY infection exhibited varying peaks of SIVsmE660 plasma RNA (10∧1-10∧6 copies/ml) that were rapidly reduced (from <13 - 440 copies/ml) within 8-10 weeks. All control PTM exhibited high levels of setpoint viremia (10∧5-10∧6 copies/ml). In contrast, PTM challenged at approximately 30 weeks after ΔGY infection became viremic with SIVsmE660, although at levels ~3 logs lower than co
**Conclusion:** While longer follow-up of these animals will be required, our data thus far demonstrate 1) ΔGY infection induces potent cellular immunity that in long-term elite controllers are capable of controlling a heterologous and highly pathogenic SIV challenge; and 2) that the determinants of this immune control may require time to mature. The development of immune responses that are not dependent on neutralizing antibodies and can lead to robust protection over time offers a unique opportunity to dissect immunological mechanisms of protection that may provide important concepts for the development of effective vaccines.

## 241 TEMPORAL ASSOCIATIONS OF B AND T CELL IMMUNITY IN A 16-WEEK INTERVAL BNT162b2 REGIMEN

**Manon Nayrac**[1], Mathieu Dubé[1], Gérémy Sannier[1], Alexandre Nicolas[1], Alexandra Tauzin[1], Olivier Tastet[1], Shang Yu Gong[1], Lorie Marchitto[1], Nathalie Brassard[1], Guillaume Beaudoin-Bussières[1], Jonathan Richard[1], Cécile Tremblay[1], Valérie Martel-Laferrière[1], Andrés Finzi[1], Daniel E. Kaufmann[1]
*[1]Centre de Recherche du CHUM, Montreal, Canada*

**Background:** Spacing of the BNT162b2 mRNA doses beyond the standard 3-week interval raised concerns about vaccine efficacy. We longitudinally analyzed B cell, T cell and humoral responses to two BNT162b2 mRNA doses administered 16 weeks apart in 43 SARS-CoV-2 naïve and previously-infected (PI) donors. We examined blood samples at five time points from baseline to 4 months post second dose.
**Methods:** We used high-parameter flow cytometry to study: i) receptor binding domain (RBD)-specific B cells; ii) Spike (S)-specific CD4 and CD8 T cells by activation-induced marker (AIM) assay; iii) S-specific CD4 and CD8 T cells by intracellular staining (ICS) assay. We measured humoral responses by ELISA, neutralization and ADCC assays. We did supervised and unsupervised (FlowSOM) analyses of B and T cell subsets, and temporal association analyses.

**Results:** We observed partial attrition of B and T cell responses between doses at a memory time point 12 weeks post first dose. RBD-specific B cell kinetics differed between cohorts: the first dose led to their robust increase in PI but small magnitude in naïve. The second dose had little effect in PI but briskly expanded RBD-specific B cells in naïve, leading to convergence between cohorts. Robust T cell responses, with a dominance of CD4 over CD8 responses, were universally induced and did not significantly differ in magnitude after either dose, although there was a trend for a gain in CD8 responses after the second dose in naïve. Unsupervised and supervised analyses of S-specific CD4 T cells showed that the first dose was sufficient to generate highly diverse CD4 subsets, including robust populations of follicular T helper cells. The second dose did not elicit new subsets but lead to convergent phenotypic and functional profiles between PI and naïve with qualitative shifts. Integrated analyses of antigen-specific responses showed immune component-specific associations over-time, with early CD4 responses post-first dose (but not at late time points) strongly correlating with B cell responses after the second dose. In contrast, CD8 responses post second dose correlated with CD4 responses at the same time point.
**Conclusion:** The 16-week interval schedule is associated with robust, multi-faceted recall cellular responses after the second dose, consistent with highly functional immune memory. The early induction of robust CD4 responses and their associations with longer-term B cell and humoral immunity support their central role in the efficacy of this vaccine regimen.

## 242 A LONG-INTERVAL VACCINE REGIMEN LEADS TO STRONG HUMORAL RESPONSES AGAINST SARS-CoV-2

**Alexandra Tauzin**[1], Shang Yu Gong[1], Guillaume Beaudoin-Bussières[1], Lorie Marchitto[1], Annemarie Laumaea[1], Manon Nayrac[1], Gérémy Sannier[1], Renée Bazin[2], Jonathan Richard[1], Marceline Côté[3], Cécile Tremblay[1], Ralf Duerr[4], Valérie Martel-Laferrière[1], Daniel E. Kaufmann[1], Andrés Finzi[1]
*[1]Centre de Recherche du CHUM, Montreal, Canada, [2]Héma-Québec, Québec, Canada, [3]University of Ottawa, Ottawa, Canada, [4]New York University, New York City, NY, USA*

**Background:** While the standard regimen of the BNT162b2 mRNA vaccine includes two doses administered three weeks apart, some public health authorities decided to space them in a context of vaccine scarcity. This decision raised concerns about vaccine efficacy, notably against the many circulating variants. In this study, we analyzed the longitudinal humoral responses from before the first dose to 4 months after the second dose in a cohort of SARS-CoV-2 naïve and previously infected (PI) individuals, with an interval of sixteen weeks between the two doses. We compared these responses to those elicited in individuals receiving the three weeks dose interval.
**Methods:** We measured the level of antibodies recognizing SARS-CoV-2 Spike or its receptor-binding domain, and the capacity of these antibodies to neutralize several variants of concern (VOCs) and other human coronaviruses. We also measured B cell responses and Fc-mediated effector functions (ADCC) elicited by vaccination.
**Results:** We observed that in PI individuals, the first dose led to strong humoral responses that could not be significantly improved further upon administration of a second dose. In the naïve individual's group, the first dose induced weak neutralizing activity but strong Fc-mediated functions and the administration of the second dose 16 weeks after led to a significant increase of humoral responses, achieving similar levels to those measured in PI individuals. In both groups, we observed that plasmas were able to recognize and neutralize the Spike of different VOCs but also SARS-CoV-1.
**Conclusion:** Our results show that individuals that received the extended BNT162b2 vaccine interval developed strong humoral responses. For the naïve donors, these responses were superior to those elicited by the three-week dose interval and comparable to the PI responses after one or two doses.

## 243 IMMUNE RESPONSES AFTER ChAdOx1 OR BNT162b2 BOOSTERS IN PRIMARY CORONAVAC VACCINATION

**Watsamon Jantarabenjakul**[1], Pimpayao Sodsai[1], Napaporn Chantasrisawad[2], Anusara Jitsatja[2], Vichaya Ruenjaiman[1], Jiratchaya Sophonphan[3], Supaporn Wacharapluesadee[2], Thanyawee Puthanakit[1], Nattiya Hirankarn[1], Opass Putcharoen[1]
*[1]Chulalongkorn University, Bangkok, Thailand, [2]King Chulalongkorn Memorial Hospital, Bangkok, Thailand, [3]Thai Red Cross AIDS Research Center, Bangkok, Thailand*

**Background:** Inactivated SARS-CoV-2 vaccine (CoronaVac) is commonly used in national immunization programmes. However, an immune response of CoronaVac significantly declined after 3 months, our study, thus, aimed to explore the immune response against COVID-19 following the booster dose by assessing both B-cell and T-cell activities compared to the convalescent samples.
**Methods:** In this prospective cohort study, 98 healthcare workers with a 2-dose CoronaVac vaccination with a subsequent booster dose of ChAdOx1 nCoV-19 (n=56) or BNT162b2 (n=42) were included during March and October 2021. Immune responses were evaluated by surrogated viral neutralization test (sVNT, cPass™), anti-SARS-CoV-2 RBD total antibodies (Elecsys®) and the ELISPOT with spike (S1) peptide pools. The samples were analyzed at baseline, 4 and 12 weeks after the second CoronaVac and 4 weeks after a booster dose. In addition, convalescent sera and peripheral blood mononuclear cells (PBMCs) of the COVID-19 patients were collected at 4 weeks after diagnosis.
**Results:** Median (interquartile range, IQR) age was 40 (31-52) years old with female predominant (80%). The median (IQR) interval after the second CoronaVac was 88 (74-92) days for ChAdOx1 nCoV-19 and 113 (112-115) days for BNT162b2. There was a significant decrease in neutralizing antibodies at the 12th week after primary CoronaVac vaccination (Figure 1). At 4 weeks after the ChAdOx1 nCoV-19 booster, median (IQR) level of sVNT and anti-RBD total antibody levels were 98.1% (97.9-98.2%) and 7768 (5349-11142), respectively, which were significantly different from the BNT162b2 booster, 98.5% (98.5-98.6%) and 25129 (17531-39434) BAU/mL, respectively (p<0.001 both). The antibody levels of the booster vaccine group were significantly higher than in the COVID-19 patients, which median (IQR) of sVNT was 80.8% (61.7-94.2%) in the mild COVID-19 and 93.8% (85.4-95.6%) in COVID-19 pneumonia, while anti-RBD total antibody levels were 94 (22-207) and 222 (130-378) BAU/mL, respectively. Using the ELISPOT with S1 peptide pools, median (IQR) of T cell response was 106 (24-256) and 196 (60-244) Spot Forming Unit (SFU)/millions of PBMCs for ChAdOx1 nCoV-19 and BNT162b2, respectively (p 0.49) which were comparable to the COVID-19 cases.
**Conclusion:** A 2-dose CoronaVac followed by ChAdOx1 nCoV-19 or BNT162b2 effectively boosted a significantly higher antibody response than the natural COVID-19 infection. In addition, BNT162b2 booster induced significantly higher antibody levels than ChAdOx1 nCoV-19.

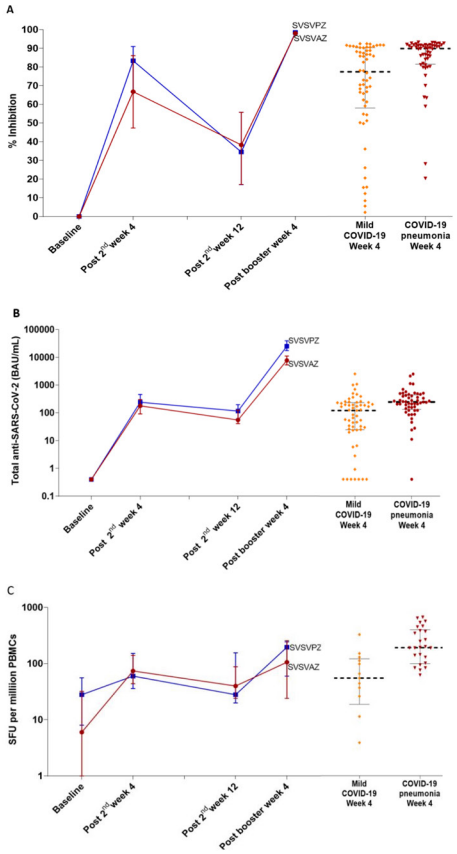



**Figure 1**. Immune responses in participants as evaluated by (A) SARS-CoV-2 surrogate virus neutralization test, (B) anti-SARS-CoV-2 total antibodies using Elecsys and (C) SARS-CoV-2 specific T-cell response using ELISPOT against spike peptide pool, at baseline, 4 and 12 weeks after 2-dose CoronaVac (SV) and 4 weeks after a booster dose of either ChAdOx1 nCoV019 (AZ) or BNT162b2 (PZ) compared to convalescent sera and PBMCs of mild COVID-19 and COVID-19 pneumonia cases at 4 weeks after diagnosis (Abbreviations: SVSVPZ indicates the 2-dose CoronaVac and the PZ booster and SVSVAZ indicates the 2-dose CoronaVac and the AZ booster.)

**244 INTRADERMAL AND INTRAMUSCULAR ADMINISTRATION OF THE BOOSTER COVID-19 VACCINATION**

**Suvimol Niyomnaitham**[1], Somruedee Chatsiricharoenkul[1], Nasikarn Angkasekwinai[1], Sansnee Senawong[1], Kulkanya Chokephaibulkit[1]
[1]*Mahidol University, Bangkok, Thailand*

**Background:** The 2-dose inactivated COVID-19 vaccine manufactured by Sinovac (CoronaVac) and viral vector COVID-19 vaccine by AstraZeneca (ChAdOx1) may not be effective in preventing Delta variant particularly after several month due to antibody decline. A 3rd dose as a booster is needed to maintain adequate antibody levels. Intradermal route is found highly immunogenic and would increase accessibility in the time of vaccine shortage.
**Methods:** This prospective study conducted in volunteers who had received 2 doses of CoronaVac and ChAdOx1 for 6-12 weeks earlier. We investigated the immunogenicity of a booster vaccination by intramuscular administration (IM) of ChAdOx1, BNT162b2 [15 µg], and BNT162b2 [30 µg]; and compare these with the 1/5 IM doses by intradermal (ID) route of ChAdOx1 (1x1010 viral particles, 0.1 ml) and BNT162b2 [5 µg]. The level of anti-SARS-CoV-2 receptor binding domain (RBD) IgG were measured by chemiluminescent microparticle immunoassay (CMIA; Abbott Laboratories Ltd.) on the day of booster vaccination and 14 days after.
**Results:** Among those received prior 2-dose CoronaVac, the geometric mean (GM) anti-SARS-CoV-2 RBD IgG level was highest following 30 µg BNT162b2 IM boosting (5,152 BAU/mL) and followed by 15 µg BNT162b2 IM (3,981 BAU/mL). The anti-SARS-CoV-2 RBD IgG GM level following the ID administration of 5 µg BNT162b2 was 3,209 BAU/mL, which is not significantly different from the 15 µg BNT162b2 IM. The IgG GM level induced by ChAdOx1 ID administration (2,810 BAU/mL) was higher than IM administration (1,358 BAU/mL). The anti-RBD IgG following booster vaccination in those prior received 2-dose ChAdOx1 primary series. Following the 30 µg BNT162b2 IM, the anti-RBD IgG GM level was highest (2,377 BAU/mL). The level induced by 15 µg BNT162b2 IM (1,962 BAU/mL) was not different from that by 5 µg BNT162b2 ID (1,490 BAU/mL). The homologous 3rd dose ChAdOx1 IM and ID induced low antibody levels. Interestingly, the anti-RBD IgG levels after the 3rd dose booster in ChAdOx1 prime were generally lower than those in CoronaVac prime series.
**Conclusion:** Heterologous boosting with BNT162b2 or ChAdOx1 induced high anti-RBD IgG levels. The intradermal route using 1/5 of intramuscular dose induced 25-156 times higher than pre-boost level, 8-31 times of the levels after 2-dose CoronaVac, and 5-8 times of that after 2-dose ChAdOx1.

**245 DURABILITY AND BOOSTABILITY OF Ad26.COV2.S IN RHESUS MACAQUES**

New Investigator Scholar

**Xuan He**[1], Abishek Chandrashekar[1], Jingyou Yu[1], Katherine McMahan[1], Frank Wegmann[2], Huahua Wan[1], Daniel Sellers[1], Jinyan Liu[1], Michelle Lifton[1], Hanne Andersen[3], Mark G. Lewis[3], Galit Alter[4], Hanneke Schuitemaker[2], Roland Zahn[2], Dan Barouch[1]
[1]*Beth Israel Deaconess Medical Center, Boston, MA, USA,* [2]*Janssen Vaccines & Prevention, Leiden, Netherlands,* [3]*BIOQUAL, Inc, Rockville, MD, USA,* [4]*Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA*

**Background:** Ad26.COV2.S is a single-shot vaccine that has demonstrated clinical efficacy against symptomatic COVID-19. In this study, we report the durability of immune responses in 20 rhesus macaques received single-shot Ad26.COV2.S and the immunogenicity of a booster shot at 8-10 months following the initial immunization.
**Methods:** Animals were immunized by intramuscular route with 1011 vp (N=10) or 5x1010 vp (N=10) Ad26.COV2.S and were followed for either 230 or 315 days. Animals were then boosted with 5x1010 vp Ad26.COV2.S (N=10). Humoral immune responses including RBD-specific Ig ELISA and pseudovirus-based virus neutralization response were monitored. Circulating RBD-specific memory B cells and bone marrow plasma cells were assessed by multiparameter flow cytometry.
**Results:** Ad26.COV2.S elicited robust and comparable RBD-specific binding and neutralizing antibody responses in animals that received the 1011 vp and 5x1010 vp doses, which peaked on days 28-56, and then showed a biphasic decay. All animals showed binding antibody responses for the duration of follow-up, and 17 of 20 animals showed neutralizing antibody responses by day 230-315. RBD-specific memory B cell response peaked on day 14-28 followed by a gradual decline, and remained detectable in 17 of 20 animals by day 230-315. On day 315 following vaccination, bone marrow RBD-specific PCs were detected in the majority of vaccinated macaques, including in all animals that received the 1011 vp dose. Following Ad26.COV2.S boost immunization, RBD-specific binding antibody responses increased 31-69 fold compared with pre-boost levels against the ancestral (WA1/2020), alpha (B.1.1.7), beta (B.1.351), kappa (B.1.617.1), and delta (B.1.617.2) SARS-CoV-2 variants. Neutralizing antibody responses increased 23-43 fold compared with pre-boost levels against the ancestral, alpha, beta, gamma (P.1), kappa, and delta SARS-CoV-2 variants. Antigen-specific memory B cell response also increased 8 fold following the boost immunization.
**Conclusion:** Ad26.COV2.S elicited durable antibody and B cell responses, and a late boost with Ad26.COV2.S resulted in a dramatic increase in humoral immunity that were highly cross-reactive across multiple SARS-CoV-2 variants in rhesus macaques. These data contribute to our understanding of Ad26.COV2.S durability and boostability, and provide important data to inform COVID-19 vaccine boosting strategies in humans.

**246 SmRNA PRIME S+N DNA BOOST VACCINATION ELICITS ROBUST IMMUNE RESPONSES IN MICE**

**Adrian Rice**[1], Mohit Verma[1], Emily Voigt[2], Peter Battisti[2], Sam Beaver[2], Kyle Dinkins[1], Shivani Mody[1], Wendy Higashide[1], Brett Morimoto[1], Elizabeth R. Gabitzsch[1], Jeffrey T. Safrit[1], Patricia R. Spilman[1], Christopher Fox[2], Corey Casper[2], Patrick Soon-Shiong[1]
[1]*ImmunityBio, Inc., Culver City, CA, USA,* [2]*Infectious Disease Research Institute, Seattle, WA, USA*

**Background:** Currently available COVID-19 vaccination regimens in the US deliver either a homologous spike (S) mRNA prime-boost or a prime-only S DNA adenovirus-vectored antigen to elicit humoral and cell-mediated responses to confer protection against SAR-CoV-2 infection. Alternatively, heterologous vaccination using two different platforms has the potential to enhance and expand immune protection. Addition of a second SARS-CoV-2 antigen, the nucleocapsid (N) protein that is less subject to mutation and elicits vigorous T-cell responses, may also be advantageous. We report immunological responses to homologous and heterologous prime-boost vaccination regimens with a human DNA adenovirus serotype 5 S plus N (AdS+N) and/or a self-amplifying S-only mRNA vaccine (AAAH) delivered with a nanostructured lipid carrier (NLC).
**Methods:** CD-1 mice received homologous or heterologous prime - boost combinations of AdS+N and AAAH. Priming doses were administered on Day 0, booster doses were delivered on Day 21, and mice were euthanized for blood and organ collection on Day 35. Serum was analyzed for anti-S (both wild type and variant) and anti-N IgG subtypes by ELISA. Spleen-resident CD4+ and CD8+ T cells were tested for IFN-γ, TNF-α, and IL-2 production in response to S-WT, S Delta variant and N protein overlapping peptides by intracellular cytokine staining (ICS). Splenocyte cytokine secretion upon stimulation with S-WT/N peptides was also assessed by IFN-γ and IL-4 ELISpot. Serum neutralization of the original Wuhan strain, Delta, and B.1.351 variants was assessed by a pseudovirus neutralization assay.
**Results:** The highest humoral and T-cell responses were seen with the heterologous AAAH prime - AdS+N boost regimen, with a significant increase in T-cell responses relative to homologous vaccination. S protein-binding IgG was similar between wild type and Delta variant S proteins, with a strong/clear Th1/Th2 bias, and T cells responded to S wild type and S Delta peptides with similar levels of cytokine expression. Sera from AAAH prime - AdS+N boost mice showed the ability to neutralize Wuhan D614G, Delta, and B.1.351 (South Africa) variant pseudoviruses at high levels.
**Conclusion:** Heterologous vaccination with the AAAH RNA vaccine prime and an AdS+N DNA boost may provide substantially improved humoral and cell-based immunity against SARS-CoV-2 variants by leveraging the advantages of each vaccine platform technology and by inclusion of immune responses to N.

**247 PROTECTIVE EFFICACY OF A GASTROINTESTINAL SARS-CoV-2 VACCINE**

New Investigator Scholar

**Jingyou Yu**[1], Natalie Collins[2], Hanne Andersen[3], Christian Hofer[4], Donald S. Burke[5], Erica K. Barkei[4], Hannah King[6], Diane Bolton[6], Kayvon Modjarrad[4], Nelson L. Michael[4], Dan Barouch[1]
[1]*Beth Israel Deaconess Medical Center, Boston, MA, USA,* [2]*Walter Reed National Military Medical Center, Bethesda, MD, USA,* [3]*BIOQUAL, Inc, Rockville, MD, USA,* [4]*Walter Reed Army Institute of Research, Silver Spring, MD, USA,* [5]*University of Pittsburgh, Pittsburgh, PA, USA,* [6]*Henry M Jackson Foundation, Bethesda, MD, USA*

**Background:** SARS-CoV-2 remains a global threat, despite the rapid deployment but limited coverage of multiple vaccines. Alternative vaccine

strategies that have favorable manufacturing timelines, greater ease of distribution and improved coverage may offer significant public health benefits, especially in resource-limited settings. Live oral vaccines have the potential to address some of these limitations; however no studies have yet been conducted to assess the immunogenicity and protective efficacy of a live oral vaccine against SARS-CoV-2. Thus far, we assessed whether oral administration of live SARS-CoV-2 in non-human primates might offer prophylactic benefits.
**Methods:** In this study, we assessed the immunogenicity of gastrointestinal (GI) delivery of SARS-CoV-2 and the protective efficacy against intranasal and intratracheal SARS-CoV-2 challenge in rhesus macaques. Esophagogastroduodenoscopy (EGD) administration of 10^6 50% Tissue Culture Infectious Dose (TCID50) of SARS-CoV-2 elicited low levels of serum neutralizing antibodies (NAb), which correlated with modestly diminished viral loads in nasal swabs (NS) and Bronchoalveolar Lavage (BAL) post-challenge. In addition, mucosal NAb titers from the rectal swabs (RS), NS, and BAL and Spike-specific T-cell responses appear to be below the limit of detection post-vaccination. Replicating virus was only observed in 44% of macaques and on limited number of dates post vaccination, suggesting limited, if any, productive infection in the GI tract.
**Results:** We demonstrate that GI delivery of live 1x10^6 TCID50 SARS-CoV-2 elicited modest immune responses and provided partial protection against intranasal and intratracheal challenge with SARS-CoV-2. Moreover, serum neutralizing antibody titers correlated with protective efficacy.
**Conclusion:** These data provide proof-of-concept that an orally administered vaccine can protect against respiratory SARS-CoV-2 challenge, but the limited immunogenicity and protective efficacy observed here suggests that the oral vaccine approach will require optimization.

### 248 LONG-TERM IMMUNOGENICITY AND EFFECTIVENESS OF CD40-TARGETING VACCINATION IN COVID-19

**Véronique Godot**[1], Lea Dupaty[1], Florence Picard[1], Ana Zarubica[2], Amandine Sansoni[2], Sylvain Cardinaud[1], Sandra Zurawski[3], Craig Fenwick[4], Mireille Centlivre[1], Mathieu Surenaud[1], Christine Lacabaratz[1], Giuseppe Pantaleo[4], Bernard Malissen[2], Gerard Zurawski[3], Yves Levy[1]
*[1]Vaccine Research Institute, Créteil, France, [2]CIPHE/Centre d'Immunologie de Marseille-Luminy, Marseille, France, [3]Baylor Institute for Immunology Research, Dallas, TX, USA, [4]Lausanne University Hospital, Lausanne, Switzerland*

**Background:** Following natural infection or vaccination, the generation of stem cell-like memory T (Tscm) cells is essential for long-term protective immunity to the virus. Tscm cells have the capacity for self-renewal and multipotency. In SARS-CoV2 infection, the emergence of CD8+ Tscm cells is correlated with the number of symptom-free days. The development of a COVID-19 vaccine able to generate CD8+ Tscm cells is of the utmost importance 1) since the emergence of SARS-CoV2 variants of concerns requires maintaining strong and long-lasting immune responses, 2) as an efficient alternative in immunocompromised people who have difficulties raising humoral immune responses.
**Methods:** We have developed a new Dendritic Cell-based vaccine composed of a humanized αCD40 monoclonal antibody fused to the RBD protein in its C-terminal Fc-domains and three T cell epitopes spanning sequences from S and N proteins in its light chains (αCD40-CoV2). Previous studies have shown that this platform elicited durable and robust T- and B-cell responses and is currently in phase I clinical development in HIV. We tested the capacity of two injections of the vaccine (10ug, i.p) given with or without poly(IC) (50ug, i.p) at 3 weeks apart to i) elicit human (hu) B-, and huT-cell responses in NSG mice reconstituted with a Human Immune System (HIS mice), ii) protect against SARS-CoV2 infection in the hCD40xK18hACE2 transgenic mice.
**Results:** We performed AIM assays and intracellular staining on spleen cells of HIS mice stimulated with overlapping peptide pools spanning the sequences of vaccine antigens. We found that both non-adjuvanted and adjuvanted vaccine efficiently induced SARS-CoV2-specific Th1 huCD4+ and huCD8+ T cells in all vaccinees compared to mock animals. SARS-CoV2-specific huCD4+ T cells were polyfunctional. We confirmed the presence of RBD-specific huCD8+ T cells in the vaccinated animals using HLA-I tetramers. A significant proportion of the multimer+ huCD8+ T cells were Tscm (CD45RA+ CD62L+ CD95+) cells in both vaccinated groups. Besides, we detected significant amounts of spike-IgG+ switched huB cells in all vaccinees. In SARS-CoV2 challenge experiments, we further showed that both vaccination settings significantly protected animals with a survival rate of 100%.
**Conclusion:** We demonstrate that the targeting of SARS-CoV-2 epitopes to CD40 induces significant B and T cells with a long-term memory phenotype in HIS mice and the ability of the vaccine to ensure complete protection against SARS-CoV2 infection.

### 249 ARMY LIPOSOMAL SPIKE FERRITIN NANOPARTICLE VACCINE INDUCES DURABLE IMMUNE RESPONSES

**Shikha Shrivastava**[1], Joshua M. Carmen[2], Zhongyan Lu[3], Rajeshwer S. Sankhala[1], Shraddha Basu[1], Alexander Anderson[2], Hung V. Trinh[1], Gary R. Matyas[2], Nelson L. Michael[2], M. G. Joyce[1], Kayvon Modjarrad[2], Jeffrey R. Currier[2], Elke Bergmann Leitner[2], Allison M. Malloy[3], Mangala Rao[2]
*[1]Henry M Jackson Foundation, Silver Spring, MD, USA, [2]Walter Reed Army Institute of Research, Silver Spring, MD, USA, [3]Uniformed Services University of the Health Sciences, Bethesda, MD, USA*

**Background:** Immunization strategies that rapidly modulate appropriate and precise interactions between the innate and adaptive immune responses are essential to generate robust, durable, and protective immunity against pathogens. Here, we describe a novel vaccine platform, Spike Ferritin Protein Nanoparticle (SpFN) mixed with the adjuvant Army Liposome Formulation containing QS-21 (ALFQ) and assessed the vaccine-induced immune signatures.
**Methods:** C57BL/6 mice were vaccinated with SpFN formulated with either Alhydrogel (SpFN+AH) or ALFQ (SpFN+ALFQ) and immunological assessment from the vaccine draining lymph nodes (dLNs), lung and spleen was performed to assess cellular engagement and cytokine activation induced by the distinct vaccine-adjuvant combinations using ELISA, flow cytometry, multiplex cytokine assay, ELISPOT, Biacore, and immunohistochemistry-based methods.
**Results:** SpFN+ALFQ significantly increased the recruitment and activation of classical and non-classical antigen presenting cells (APCs) with upregulated costimulatory molecules in the dLNs. Recruitment of highly activated APCs to the dLNs of SpFN+ALFQ vaccinated mice was associated with an increased frequency of polyfunctional spike-specific memory CD4+ T cells and Kb spike (539-546)-specific long-lived memory CD8+ T cells with effective cytolytic function and distribution to the lungs. Immunohistochemistry and/or flow cytometry showed that SpFN+ALFQ induced an increase in the frequency of IL-21 secreting T follicular helper (Tfh) cells and germinal center (GCs) B cells in the dLNs and spleen, and generated spike specific antibodies as early as day 5. Increased interaction of Tfh and B cells in the GCs of SpFN+ALFQ vaccinated mice was associated with higher frequency of spike specific long-lived plasma cells in the bone marrow. Longitudinal antibody analysis showed a 10-fold higher avidity which was maintained even at week 21 post-vaccination compared to SpFN+AH.
**Conclusion:** In conclusion, SpFN+ALFQ vaccine effectively recruited highly activated multifaceted APCs driving potent antigen-specific polyfunctional T cell responses. SpFN+ALFQ caused an increase in the size and frequency of GCs and early engagement of Tfh and B cells, leading to the generation of high titer, high avidity, durable binding and neutralizing antibody responses. Together, these findings highlight the importance of ALFQ in orchestrating the interplay of innate and adaptive immune responses. Currently, SpFN+ALFQ is being evaluated in a phase I human clinical trial.

### 250 AAVCOVID: A SINGLE-DOSE, THERMOSTABLE COVID-19 VACCINE WITH DURABLE IMMUNOGENICITY

**Nerea Zabaleta**[1], Urja Bhatt[2], Cécile Herate[3], Pauline Maisonnasse[3], Jessica A. Chichester[4], Julio Sanmiguel[2], Cheikh Diop[2], Dawid Maciorowski[2], James M. Wilson[4], Roger Le Grand[3], Luk H. Vandenberghe[1]
*[1]Harvard Medical School, Boston, MA, USA, [2]Mass Eye and Ear, Boston, MA, USA, [3]IDMIT, Fontenay-aux-Roses, France, [4]University of Pennsylvania, Philadelphia, PA, USA*

**Background:** The SARS-CoV-2 pandemic has affected more than 250 million people worldwide resulting in 5 million deaths. To contain the pandemic, there is a continued need for safe vaccines that provide durable protection at low and scalable doses that easily delivered. Previously, we showed that an adeno-associated virus (AAV)-based vaccine candidate (AC1) elicited high humoral and cellular immunogenicity in mice and nonhuman primates (NHP) following a single injection, which provided near-sterilizing immunity against SARS-CoV-2 in NHP. Here, we developed optimized AAVCOVID vaccine candidates for higher potency and protection against variants of concern (VOC).
**Methods:** The promoter in AC1 vector was substituted by three different promoters to increase the expression of Spike and they were tested in mice by

single IM injection. Transgene expression and anti-Spike antibody and cellular responses were determined to assess vector potency. Then, the candidate that showed higher potency (ACM1) was engineered to express the Beta (ACM-Beta) and Delta (ACM-Delta) VOC Spike. The immunogenicity provided by ACM-Beta and ACM-Delta was characterized in mice and NHP. The cross-reactivity with the Wuhan and VOC Spikes was also assessed in the animals immunized with different Spike variants. Finally, challenge and durability studies were performed in NHPs vaccinated with the new candidates.
**Results:** Vaccination with ACM1 candidate (miniCMV promoter) resulted in 100-fold higher Spike expression and 40-fold higher antibody responses compared to the prototypic AC1 candidate in mice. When ACM1, ACM-Beta and ACM-Delta were compared in mice, we found that the immune responses against the self-transgene were not significantly different. However, cross-reactivity was different, being ACM-Delta the candidate that better cross-neutralized the different VOC. Similar results were observed in NHP: higher potency of the candidates carrying the miniCMV promoter and similar cross-reactivity profiles. Additionally, ACM-Beta showed protection against Beta SARS-CoV-2 challenge and a durability study for ACM-Delta is ongoing.
**Conclusion:** This work shows the adaptability and versatility of AAVCOVID vaccine platform to improve potency and protect against VOC. These observations together with the single, low dose requirement, high yield manufacturability, and 1-month stability for storage at room-temperature may make this technology well-suited to support effective immunization campaigns for emerging pathogens on a global scale.

## 251 SPIKE PLUS NUCLEOCAPSID VACCINE PROTECTS AGAINST SARS-CoV-2 DELTA INFECTION IN NHPs

**Nanda Kishore Routhu**[1], Sailaja Gangadhara[1], Lilin Lai[1], Ayalnesh Shiferaw[1], Stephanie Fischinger[2], Bartsch Yannic[2], Sheikh A. Rahman[1], Sherrie M Jean[3], Chelsea Wallace[3], Rachelle L Stammen[3], Pamela A. Kozlowski[4], Galit Alter[2], Mehul Suthar[5], Rama R. Amara[1]
*[1]Emory Vaccine Center, Atlanta, GA, USA, [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [3]Yerkes National Primate Research Center, Atlanta, GA, USA, [4]Louisiana State University, New Orleans, LA, USA, [5]Emory University, Atlanta, GA, USA*

**Background:** SARS-CoV-2 vaccines capable of inducing broad and cross-reactive humoral and T cell responses help to fight against emerging variants. In this study we compared the immunogenicity and efficacy of modified vaccinia Ankara (MVA) based SARS-CoV-2 vaccine expressing furin-cleavage site inactivated stabilized spike (SdFCS) and nucleocapsid (N) delivered via intramuscular (IM), buccal or sublingual (SL) routes in rhesus macaques (RMs).
**Methods:** Three groups (n=5/group) of RMs were immunized with MVA/SdFCS-N vaccine on weeks 0 and 4, via IM, buccal, or SL route. An additional group (control) received non-recombinant MVA via IM. IM vaccinations were delivered using needle and SL and buccal vaccinations were delivered using a needle-free injection device. All RMs were challenged with B.1.617.2 strain (Delta) of SARS-CoV-2 at week 8 via intratracheal and intranasal routes simultaneously. Various humoral and cellular immune parameters were determined post vaccination and challenge. SARS-CoV-2 subgenomic RNA (sgRNA) was measured to monitor virus replication in the upper (nose) and lower (lung) respiratory tract.
**Results:** IM vaccination induced strong RBD-specific IgG antibody in serum, nose, throat, lung, and rectum. The serum antibody showed strong live virus neutralizing activity against WA-1/2020 (median of 415) and B.1.617.2 strains (median of 317). Serum from IM vaccinated animals also demonstrated strong non-neutralizing effector functions such as ADCD, ADCP and ADNKA. In addition, IM vaccination induced strong CD4 and CD8 T cell response in the blood that was directed against both S and N. In contrast, the SL and buccal vaccination-induced antibody showed lower neutralization titer against WA-1/2020 (143 and 302, respectively), and showed 4.5-fold lower cross reactivity neutralization titer against B.1.617.2 compared to WA-1/2020. Following challenge with B.1.617.2, the IM group RMs showed superior protection with 3 of the 5 animals being negative in upper and lower respiratory airways at Day 2. In contrast, no significant protection was observed in the SL group. Vaccine induced neutralizing and non-neutralizing antibody effector functions showed direct association with protection.
**Conclusion:** Our findings showed that IM vaccination with improved MVA-based SARS-CoV-2 vaccine elicits cross-reactive antibody and T cell responses and protect against heterologous SARS-CoV-2 Delta challenge in RMs. They also showed IM vaccinations are superior to oral vaccinations.

## 252 INVESTIGATING CONSERVED SEQUENCE IN THE SARS-CoV-2 GENOME AS NOVEL VACCINE IMMUNOGEN

**Gabriel Dagotto**[1], John D. Ventura[1], David R. Martinez[2], Tochi Anioke[1], Benjamin S. Chung[1], Mazuba Siamatu[1], Julia Barrett[1], Jingyou Yu[1], Lisa H. Tostanoski[1], Alexandra Schaefer[2], Ralph Baric[2], Bette Korber[3], Dan Barouch[1]
*[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]Los Alamos National Laboratory, Los Alamos, NM, USA*

**Background:** It is imperative to investigate novel, broadly conserved coronavirus immunogens as new SARS-CoV-2 variants of concern are continually emerging. The goal of this study was to generate a broadly protective long-term vaccine candidate against potential new variants of SARS-CoV-2 and novel, outbreak coronaviruses. The vaccine immunogen spanned portions of the highly conserved RNA replication machinery (nsp12 and nsp13) (CoV.Con). The vaccine was packaged into a rhesus adenoviral vector (RhAd52.CoV.Con) with the goal of generating robust long-lived CD8+ T-cell responses.
**Methods:** The CoV.Con immunogen was generated by aligning coronavirus sequences to determine the most conserved region. ACE2 carrier and BALB/c mice were immunized intramuscularly with 10^9 RhAd52.CoV.Con and boosted four weeks later. Splenocytes were harvested four weeks after boost. Cellular immunity was determined through ELIspot and intracellular cytokine stain (ICS). BALB/c mice were primed and boosted with RhAd52.CoV.Con. Four weeks post boost mice were challenged intranasally with mouse adapted SARS-CoV-2. Protection was measured by weight loss and plaque assay.
**Results:** Four weeks post RhAd52.CoV.Con boost immunization, ACE2 carrier and BALB/c mice developed cellular immunity as shown by ELIspot (Fig 1a) and ICS. ACE2 carrier mice cellular immunity showed bias toward nsp12 while BALB/c mice showed nsp13 preference. BALB/c mice were primed and boosted with RhAd52.CoV.Con. Four weeks after boost mice were challenged with mouse adapted SARS-CoV-2. RhAd52.CoV.Con was compared against and combined with a suboptimal dose of RhAd52.S.pp at 4 and 8 weeks post injection. Protection against weight loss (Fig 1b) and viral load (Fig 1c) was minimal although increased RhAd52.S.pp protection was observed from 4 to 8 weeks post immunization. Increased RhAd52.S.pp protection corresponded to increased spike antibody binding and neutralizing titers.
**Conclusion:** Our work investigates a highly conserved coronavirus immunogen, CoV.Con, demonstrating immunogenicity in two mouse strains. While RhAd52.CoV.Con protection in the mouse model was minimal it demonstrates a schema for generating coronavirus immunogens that can protect against multiple different viruses. This work takes the first steps towards generating a long-lived broadly protective T-cell coronavirus vaccine.

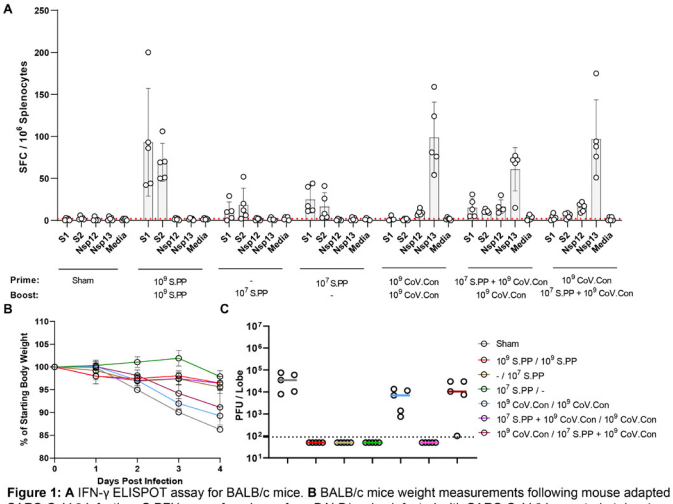



**Figure 1:** **A** IFN-γ ELISPOT assay for BALB/c mice. **B** BALB/c mice weight measurements following mouse adapted SARS-CoV-2 infection. **C** PFU assay from lungs from BALB/c mice infected with SARS-CoV-2 harvested at day 4.

## 253 ANTIGENICITY OF THE MU (B.1.621) AND A.2.5 SARS-CoV-2 SPIKES

**Debashree Chatterjee**[1], Shang Yu Gong[1], Alexandra Tauzin[1], Annemarie Laumaea[1], Guillaume Goyette[1], Gabrielle Gendron-Lepage[1], Halima Medjahed[1], Jonathan Richard[1], Sandrine Moreira[2], Marceline Côté[3], Andrés Finzi[1]

[1]Centre de Recherche du CHUM, Montreal, Canada, [2]Institut National de Sante Publique Quebec, Quebec, Canada, [3]University of Ottawa, Ottawa, Canada

**Background:** The rapid emergence of SARS-CoV-2 variants is fueling the recent waves of the COVID-19 pandemic. Recently identified Mu (B.1.621) and A.2.5 variants carry some mutations shared by other variants of concerns (VOCs). For example, N501Y and E484K mutations in the receptor-binding domain (RBD) domain detected in B.1.1.7 (Alpha), B.1.351 (Beta) and P.1 (Gamma) are now present within the Mu variant. Similarly, the L452R mutation of B.1.617.2 (Delta) variant is now present in A.2.5. Here, we evaluated the capacity of Mu and A.2.5 Spikes to interact with angiotensin-converting enzyme 2 (ACE2) and performed binding and neutralization assays with plasma from vaccinated individuals. In addition, to better understand their antigenic properties, we compared both Mu and A.2.5 with Alpha, Beta, Gamma and Delta VOCs Spikes.
**Methods:** Cells expressing the different Spikes were interrogated for their capacity to interact with the ACE2 receptor using a recombinant ACE2-Fc recombinant protein. We also evaluated their recognition by plasma from BNT162b2 vaccinated individuals. Biolayer interferometry (BLI) was used to measure the binding kinetics of selected RBD mutants to soluble ACE2 (sACE2). Finally, we evaluated the susceptibility of pseudoviral particles bearing the different Spikes to neutralization by plasma from vaccinated individuals.
**Results:** All SARS-CoV-2 S-glycoprotein variants were recognized less efficiently by plasma from vaccinated SARS-CoV-2 naïve and previously-infected individuals compared to D614G Spike with the exception of B.1.1.7 S-glycoprotein. Enhanced ACE2 interaction by the Spikes tested was associated with a decrease in the off-rate of the ACE2-RBD interaction. Pseudoviral particles bearing the Spike of Mu variant were similarly neutralized by plasma from vaccinated individuals than those carrying the Beta and Delta Spikes.
**Conclusion:** Plasma from vaccinated SARS-CoV-2 naïve and previously-infected individuals efficiently recognized all the Spikes tested. The decreased neutralization susceptibility of pseudoviral particles expressing the Mu Spike was similar to Beta and Delta, thus underscoring the importance of functionally tracking emerging variants. In summary, our results highlight the importance of measuring critical parameters such as ACE2 interaction, plasma recognition and neutralization from each emerging variant.

## 254 OPTIMIZATION OF NONCODING REGIONS IMPROVES mRNA SARS-CoV-2 VACCINE IN NHPs

**Makda Gebre**[1], Susanne Rauch[2], Nicole Roth[2], Jingyou Yu1, Abishek Chandrashekar[1], Noe B. Mercado[1], Xuan He[1], Jinyan Liu[1], Katherine McMahan[1], Amanda Martinot[3], Xiaowen Liu[4], Mark G. Lewis[5], Stefan Mueller[5], Benjamin Petsch[2], Dan Barouch[1]
[1]Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA, [2]CureVac AG, Tubingen, Germany, [3]Tufts University Cummings School of Veterinary Medicine, North Grafton, MA, USA, [4]Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA, [5]Bioqual, Rockville, MD, USA

**Background:** The CVnCoV (CureVac) mRNA vaccine for SARS-CoV-2 has recently been evaluated in a Phase IIb/III efficacy trial in humans. CV2CoV is a second-generation mRNA vaccine with optimized non-coding regions and enhanced antigen expression.
**Methods:** Here we report a head-to-head study of the immunogenicity and protective efficacy of CVnCoV and CV2CoV in nonhuman primates. We immunized 18 cynomolgus macaques with two doses of 12 ug of lipid nanoparticle formulated CVnCoV, CV2CoV, or sham (N=6/group).
**Results:** CV2CoV induced substantially higher binding and neutralizing antibodies, memory B cell responses, and T cell responses as compared with CVnCoV. CV2CoV also induced more potent neutralizing antibody responses against SARS-CoV-2 variants, including B.1.351 (beta), B.1.617.2 (delta), and C.37 (lambda). While CVnCoV provided partial protection against SARS-CoV-2 challenge, CV2CoV afforded robust protection with markedly lower viral loads in the upper and lower respiratory tract. Antibody responses correlated with protective efficacy.
**Conclusion:** These data demonstrate that optimization of non-coding regions can greatly improve the immunogenicity and protective efficacy of an mRNA SARS-CoV-2 vaccine in nonhuman primates.

## 255 IgG GLYCOSYLATION PREDICTS COVID-19 DISEASE SEVERITY AND VACCINE ANTIBODY RESPONSE

**Michelle Ash**[1], Pavan Bhimalli[1], Byoung-Kyu Cho[2], Basil Baby Mattamana[2], Stephanie Gambut[1], Imad Tarhoni[1], Cristina Fhied[1], Thomas Hope[3], Beverly Sha[1], Young Ah Goo[2], Lena Al-Harthi[1], Joao Mamede[1], Jeffrey Borgia[1], Neil Kelleher[2], Jeffrey Schneider[1]
[1]Rush University Medical Center, Chicago, IL, USA, [2]Northwestern University, Evanston, IL, USA, [3]Northwestern University, Chicago, IL, USA

**Background:** Although vaccination efforts have been deployed worldwide over the past 10 months, there are still gaps in our understanding surrounding the immune response to SARS-CoV-2 infection and vaccination, including changes to the antibody repertoire. One way of tracking the immune response over time is through measuring IgG Fc glycosylation, which provides insight into the inflammatory state of an infected individual, antibody effector function, antibody half-life, and more. Therefore we set out to interrogate bulk IgG changes in glycosylation in both natural infection and vaccinated cohorts in order to determine potential insight into protection from severe disease and responsiveness to vaccination.
**Methods:** We evaluated 98 plasma samples from COVID-19 patients with either mild or severe COVID-19. Symptomatic patients were characterized as mild or severe based on hospital admission. We also evaluated plasma from 228 vaccinated individuals (Pfizer-BioNTech). Bulk IgG glycosylation analysis was measured through a quadrupole orbitrap mass spectrometry. Neutralization potential was assessed through a spike pseudotyped neutralization assay. Spike antibody levels were measured using a Luminex assay and ELISA.
**Results:** We found that inflammatory glycans (fucosylated agalactosylated, G0F) on bulk IgG were elevated in hospitalized COVID-19 patients and increased over time in this population when compared to mild infection. Mild patients had an anti-inflammatory glycosylation pattern (afucosylated galactosylated, G2) which increased over time. Siaylation levels were elevated in mild individuals, increased over time, and correlated with increased RBD antibody levels. Interestingly, when we assessed COVID-19 vaccinated individuals with low Spike antibody levels and low neutralization, they had the same glycosylation pattern (G0F) as that of hospitalized COVID-19 patients. Additionally, a small longitudinal vaccinated cohort (out to 8 months) revealed a decrease in G0F associated with peak IgG concentrations and neutralization (Fig 1).
**Conclusion:** Inflammatory glycan signatures, such as an elevation in G0F glycans, can be used as prognostic tools, not only to predict the severity of COVID-19 disease, but also to predict patient responsiveness to COVID-19 vaccines. This is the first report identifying a shift in glycan signature to be associated with COVID-19 disease severity and vaccine responsiveness, which can guide future studies into SARS-CoV-2 protective immunity and vaccine development.

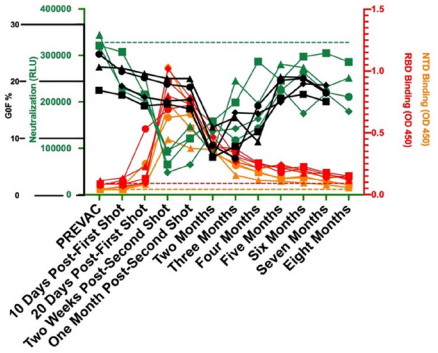



**Figure 1. Longitudinal assessment of SARS CoV2 antibody levels, neutralization potential, and Glycosylation pattern.** Four Individuals, denoted by square, triangle, diamond, and circle, were tracked up to 8 months past the second shot of Pzifer/Biontech. In red and orange are RBD and NTD antibody binding (OD450, dotted line background threshold), respectively. In green is pseudotyped neutralization entry assay, with lower RLU correlating to less entry and higher neutralization (dotted line is background). G0F glycosylation percentages (of total bulk IgG) are shown in the black lines.

**256 EVALUATING VIRUS-SPECIFIC CD8+ T CELLS FROM MULTIPLE ANATOMICAL SITES**

**Jennifer Simpson**[1], Carly E. Starke[2], Carol Vinton[1], Alexandra Ortiz[1], Amy Ransier[1], Sam Darko[1], Daniel C. Douek[1], Jason Brenchley[1]
*[1]National Institutes of Health, Bethesda, MD, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

**Background:** Antigen-specific CD8+ T cells play a key role in the host's antiviral response. T cells recognize viral epitopes via the T cell receptor (TCR), which contains the complementarity-determining region-3 (CDR3), comprising the variable, diversity and joining regions of the TCRB gene. During chronic simian immunodeficiency virus (SIV) infection of Asian macaque nonhuman primates, tissue specific clonotypes were identified among SIV-specific CD8+ T cells. Here, we sought to determine potential mechanisms responsible for the tissue-specific clonotypic structure. We examined whether the priming event and/or chronic antigen exposure is responsible for tissue specific TCR repertoires. We evaluated the TCR repertoire of SIV-specific CD8+ T cells after acute antigen exposure following inoculation with a SIV DNA vaccine and longitudinally during the acute and chronic phases of SIV infection, and after administration of antiretrovirals (ARVs). Finally, we assessed the TCR repertoire of cytomegalovirus (CMV)-specific CD8+ T cells to establish if TCR tissue-specificity is shared among viruses that chronically replicate.
**Methods:** Mamu-A*01+ or Mamu-*02+ Rhesus macaques were infected with SIV mac239 or administered with 1 mg of DNA plasmid CMV/R-SIVgag vaccine. CMV infection occurred naturally. SIV-specific CD8+ T cells were enumerated, phenotyped, and sorted by FACS from multiple anatomical sites using MHC-I Pentamers. Next generation sequencing of TCRB genes was performed to determine the clonotypic structure of antigen specific CD8+ T cells across tissues.
**Results:** TCR sequences unique to singular anatomical sites were identified after limited antigen exposure via vaccination and upon acute SIV infection. Tissue-specific clones also persisted into chronic infection and after ARV treatment, with the clonotypic structure continuing to evolve after ARV administration. Finally, tissue-specific clones were also observed in CMV-specific CD8+ T cells.
**Conclusion:** Together, these data suggest that acute antigen priming is sufficient to induce tissue specific clones and that this clonal hierarchy can persist even when antigen loads are therapeutically reduced, providing mechanistic insight into tissue-residency.

**257 CD8+ T-CELL REPROGRAMMING TO BOOST ANTI-HIV POTENTIAL**

**Federico Perdomo-Celis**[1], Caroline Passaes[1], Stevenn Volant[1], Faroudy Boufassa[2], Pierre De Truchis[2], Morgane Marcou[3], Katia Bourdic[2], Laurence Weiss[4], Corinne Jung[4], Christine Bourgeois[2], Cécile Goujard[2], Laurence Meyer[2], Michaela Müller-Trutwin[1], Olivier Lambotte[2], Asier Sáez-Cirión[1]
*[1]Institut Pasteur, Paris, France, [2]University of Paris Saclay, Paris, France, [3]University of Paris Saclay, Garches, France, [4]University of Paris, Paris, France*

**Background:** Virus-specific CD8+ T cells play a central role in HIV-1 natural controllers. They have been shown to display a distinct memory program that confers them stemness properties, high survival, polyfunctionality, proliferative capacity, metabolic plasticity, and antiviral potential. The development and maintenance of such qualities by memory CD8+ T cells thus appear crucial to achieve natural HIV-1 control. We hypothesized that targeting CD8+ T cell signaling pathways, such as Wnt/TCF-1 and mTORC, related to the maintenance of a stem-like memory profile, would reprogram the functional capacity of cells derived from HIV-1 non-controllers towards superior functional capacity.
**Methods:** Purified CD8+ T cells from people without HIV-1 or HIV non-controllers were treated ex vivo for 12 hs with a GSK3 inhibitor (hereinafter referred to as reprogramming), or free vehicle as control, followed by phenotypic, transcriptional, metabolic, and functional analyses upon polyclonal, antigen-specific, or cytokine stimulation.
**Results:** Treatment of HIV-specific CD8+ T cells from HIV non-controller individuals with the GSK3 inhibitor promoted the enrichment of less differentiated memory subsets, including TCF-1+ stem-like subsets (median [range] 0% [0-16.28] vs 32.16% [20.65-47.27] stem-like memory cells, P=0.03). Such reprogrammed cells were characterized by enhanced survival and expansion capacity upon stimulation (median [range] 0.068% [0.016-0.13] vs 0.11% [0.039-0.44], Gag-responding cells; P=0.001), and by restored metabolic plasticity and decreased mTORC1 dependency. Moreover, reprogrammed cells had superior polyfunctionality (~40-fold increase in the % of IFN-γ+ TNF-α+ IL-2+ Granzyme B+ Gag-responding CD8+ T cells upon reprogramming). They also expressed higher levels of IL-7 and IL-15 receptors and responded better to these γ-chain cytokines (median [range] 30.8% [22.5-47.5] vs 55.95% [31.5-69.1], CFSElo HIV Dextramer+ CD8+ T cells; P=0.007), revealing their enhanced potential for homeostatic self-renewal.
**Conclusion:** Ex vivo treatment of virus-specific CD8+ T cells from non-controllers with a GSK3 inhibitor resulted in reprogramming and acquisition of phenotypic, transcriptional, metabolic, and functional attributes associated with natural control of HIV-1. Thus, such CD8+ T cell reprogramming, combined with other available immunomodulators, might represent a promising strategy for adoptive cell therapy in the search for an HIV-1 cure.

**258 CD8 RESPONSE TO HIV PROVIRUS IN ELITE CONTROLLERS IMPROVES EXPECTATIONS OF HIV CURE**

**Maria A. Navarrete-Muñoz**[1], Jaime Valentin[2], José M. Ligos[3], Alfonso Cabello Úbeda[4], Miguel Górgolas[4], José M. Benito[1], Norma Rallón[1]
*[1]Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain, [2]IdiPAZ, La Paz University Hospital, Madrid, Spain, [3]Cytek Biosciences, Fremont, CA, USA, [4]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain*

**Background:** The existence of escape mutations in epitopes from the viral reservoir of HIV patients recognized by CD8 T cells poses a great challenge to viral eradication. A broad and efficient CD8 response is associated with HIV control as demonstrated by studies in HIV elite controllers. Herein, we have analysed the functionality profile of CD8 response against autologous epitopes from the viral reservoir in two groups of HIV infected patients with different mechanism of viral control (spontaneously or through cART).
**Methods:** Fourteen HIV+ patients were included: 7 elite controllers (EC) and 7 cART-suppressed (TX). Functional profile, lytic ability, maturation stage, level of exhaustion, level of activation and homing potential of CD8 T cells recognizing autologous HIV-Gag epitopes from HIV reservoir were assessed by spectral flow cytometry. Inter-group differences were tested by non-parametric tests. A canonical discriminant analysis (CDA) was carried out to find those HIV-specific CD8 T cells features that better discriminate between studied groups.
**Results:** Compared to TX group, the CD8 T cells recognizing autologous peptides from EC patients showed higher levels of effector memory cells (CD45RA-CCR7- cells) (p=0.034), and lower levels of exhaustion (PD1+Tim3+ cells) (p=0.083).The majority of CD8 response was mediated by monofunctional cells (cells producing only one cytoquine) in both groups of patients; however, MIP1b was the cytoquine mediating the response in EC patients and IFNg in TX patients. CDA model was able to clearly discriminate EC and TX groups, being exhaustion (PD1+Tim3+) of HIV-specific CD8 T cells the feature with the highest relevance in the discriminant model (coefficient=1.882, p<0.001).
**Conclusion:** Our results show that the functional profile of CD8 T cells against autologous HIV virus can distinguish between elite controllers and non-controllers patients. Importantly, low levels of exhaustion of virus-specific CD8 cells and production of MIP1b (the natural ligand of HIV-coreceptor CXCR5 with anti-viral properties) were among the most important factors associated to the EC status. Taken together, these results suggest that HIV-specific CD8 response in EC patients could be able to kill latently infected cells after reactivation with latency reversing agents, which open a new opportunity to HIV eradication.

**259 HIGHLY DAMPENED HIV-SPECIFIC CYTOLYTIC T-CELL RESPONSE DEFINE VIREMIC NONPROGRESSION**

**Amit Kumar Singh**[1], Varsha Padwal[1], Harsha Palav[1], Shilpa Velhal[1], Vidya Nagar[2], Priya Patil[2], Vainav Patel[1]
*[1]National Institute for Research in Reproductive Health, Mumbai, India, [2]Grant Medical College, Mumbai, India*

**Background:** Viremic Non-Progressors (VNPs) are a distinct group of HIV-1 infected individuals who remain asymptomatic for several years (>7 years) and have good preservation of CD4 count without ART treatment but display high viral replication. We recently reported that CD4 central memory preservation along with intact thymic repopulation are key homeostatic mechanism resisting CD4 depletion in VNPs. In this study we attempted to identify gut trafficking potential and virus specific functional attributes that could underlie the paradoxical virus-host equilibrium observed in VNPs.
**Methods:** We analyzed HIV-specific responses in VNPs, Viremic Controllers (VC) and Putative Progressors (PuPs) with recent HIV1 infection. All groups had CD4 count of ≥500 cells/µl and had high viral replication except for VCs (Table1).

Five different functions, including production of IFN-γ, IL-2, TNF-α, MIP-1β and CD107a expression in different memory CD4 and CD8 T cell subsets were evaluated following stimulation of thawed PBMCs with overlapping HIV1 Gag and Env peptides. In addition, ex-vivo immunophenotyping was performed to understand CCR5 (HIV Co-receptor) and integrin α4β7 (Gut trafficking marker) level on different CD4 and CD8 T cell subsets. Non-parametric one-way ANOVA test was performed on the data.

**Results:** Our study delineates unique signatures of viremic non-progression where HIV-specific T cell responses in VNPs are dominated by a potent non-cytolytic response enriched for MIP-1β production with concomitantly dampened degranulation ability (CD107a detection; cytolytic potential). VCs who efficiently control viremia, also had robust cytolytic potential. Intriguingly, early response in PuPs shared both these features but lacked Gag-specific CD4 central memory IFN-γ responses (CD4 help) compared to both VNP and VC groups. Polyfunctional response observed in VNPs were quantitatively and qualitatively comparable to both VC and immunologically competent (≥500 CD4 cells/μl) PuP groups. Additionally, ex-vivo immunophenotyping showed different CD4 subsets had similar CCR5 expression. Intriguingly, in addition to diminished cytolytic potential, VNPs also had significantly reduced frequency of α4β7 expressing CD8 memory subsets suggesting relatively less trafficking of CTLs in GALT and possibly reduced gut pathology.

**Conclusion:** Understanding detailed mechanisms underlying the non-cytolytic HIV-specific T cell response mediated non-progression in VNPs may allow immunotherapeutic interventions to achieve functional cure.

**Table 1: Clinical characteristics of the study participants**

| | Viremic Controllers [VCs, n= 07] | Viremic Non-Progressors [VNPs, n= 12] | Putative Progressors [PuPs, n= 11] |
|---|---|---|---|
| Age[a] (Years), Range | 42 (29-60) | 39 (30-49) | 35 (21-59) |
| Gender | Female = 03<br>Male = 04 | Female = 04<br>Male = 08 | Female = 06<br>Male = 05 |
| CD4+ T cell count[a] (cells/μl), Range | 900<br>(501- 1469) | 680<br>(501 - 910) | 553<br>(514-908) |
| Viral Load ($log_{10}$ copies/ml), Range | 2.95<br>(1.73-3.04) | 4.73<br>(4.01-5.35) | 4.71<br>(3.58-5.98) |
| Duration of infection[a] (Years), Range | 10<br>(8 - 24) | 10<br>(7 - 16) | 1<br>(0.5 – 03) |
| Antiretroviral therapy (ART) status | Naïve | Naïve | Naïve |

[a]Data are expressed as the median (range)

## 260 T CELLS EXPRESSING MULTIPLE INHIBITORY RECEPTORS PERSIST ON LONG-TERM ART

**Bernard J. Macatangay**[1], Deborah K. McMahon[1], Hanna Mar[2], Ronald J. Bosch[2], Joshua Cyktor[1], Ann C. Collier[3], Sharon A. Riddler[1], Evelyn Hogg[4], Joseph J. Eron[5], John W. Mellors[1], Rajesh T. Gandhi[6], Charles R. Rinaldo[1]

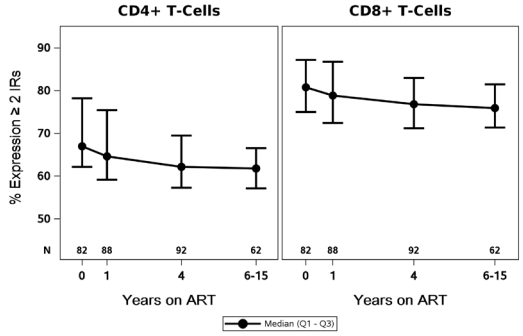
*[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University of Washington, Seattle, WA, USA, [4]ACTG Network Coordinating Center, Silver Spring, MD, USA, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]Massachusetts General Hospital, Boston, MA, USA*

**Background:** Expression of multiple inhibitory receptors (IR) is associated with T cell exhaustion in chronic viral infections. We evaluated frequencies of T cells expressing ≥2 IR among people with HIV (PWH), declines on ART and in HIV(-) individuals.

**Methods:** Using flow cytometry, we assessed expression of 6 IRs (PD1, PDL1, TIM3, LAG3, CTLA4, and TIGIT) on CD8+ and CD4+ T cells in samples pre-ART and at 1, 4, and 6-15 years of suppressive ART among PWH and from age-matched HIV(-) controls. Boolean analysis assessed the 64 different IR combinations. Frequencies of T cells expressing multiple (≥2) IRs on ART were compared with HIV(-). Levels of T cell activation and soluble inflammatory markers were measured using flow cytometry and ELISA, respectively.

**Results:** We evaluated 95 PWH (median age 39 at ART initiation; 79% male) and 20 HIV(-) individuals (median age 42; 75% male). Among PWH, a median of 80.8% of CD8+ T cells and 67.0% of CD4+ T cell expressed ≥2 IR pre-ART (Figure). In 68% of participants, frequencies decreased on CD8+ T cells from pre-ART to year 1 of ART ($p<0.01$; sign test); in 73% of participants, frequencies decreased on CD4+ T cells ($p<0.01$). Frequencies further decreased between 1 and 4 years of ART (decreased in 66% of participants on CD8+ T cells and in 74% on CD4+ T cells; $p<0.01$), then stabilized between 4 and 6-15 years on ART. Frequencies of T cells expressing multiple IR pre-ART strongly correlated with frequencies on ART (r=0.44-0.79; $p<0.01$; Spearman). Compared to HIV(-) individuals, PWH who had been on-ART for 4 years continued to have higher frequencies of CD8+ T cells expressing ≥2 IR (median=76.9% in PWH vs 73.5% in HIV(-); p=0.02). In contrast, frequencies of CD4+ T cells expressing ≥2 IR were similar at year 4 of ART in PWH and people without HIV. Levels of T cell activation at year 4 on-ART (HLA-DR/CD38) correlated with frequencies of CD8+ T cells expressing ≥2 IR (r=0.22; p=0.04), but less so with CD4+ T cell frequencies (r=0.15; p=0.16). Multiple IR expression on CD8+ T cells modestly correlated with plasma IL-6 (r=0.20; p=0.06) and soluble CD14 (r=0.18; p=0.09).

**Conclusion:** Despite sustained suppression of plasma viremia, CD8+ T cells among PWH continue to express multiple IR at frequencies higher than age-matched people without HIV. Frequencies of T cells expressing multiple IR before ART strongly correlate with those on ART suggesting an immune dysregulation legacy effect. Persistence of these T cells may affect responses to immunotherapies targeting single IR.




## 261 INHIBITORY RECEPTOR EXPRESSION CORRELATES WITH HIV PERSISTENCE AND IMMUNE RESPONSES

**Bernard J. Macatangay**[1], Deborah K. McMahon[1], R. Brad Jones[2], Adam R. Ward[2], Hanna Mar[3], Ronald J. Bosch[3], Joshua Cyktor[1], Sharon A. Riddler[1], Ann C. Collier[4], Evelyn Hogg[5], Joseph J. Eron[6], John W. Mellors[1], Rajesh T. Gandhi[7], Charles R. Rinaldo[1]

*[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Weill Cornell Medicine, New York, NY, USA, [3]Harvard TH Chan School of Public Health, Boston, MA, USA, [4]University of Washington, Seattle, WA, USA, [5]ACTG Network Coordinating Center, Silver Spring, MD, USA, [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [7]Massachusetts General Hospital, Boston, MA, USA*

**Background:** T cell expression of inhibitory receptors (IR) has been associated with measures of HIV persistence and immune responses to HIV. In a cohort of persons with HIV (PWH) with suppressed plasma viremia on ART for at least 4 years, we evaluated which specific combinations of IR were associated with HIV persistence and HIV-specific immune responses.

**Methods:** Using flow cytometry, we measured frequencies of CD4+ and CD8+ T cells expressing combinations of 6 different IR: PD1, PDL1, TIM3, CTLA4, TIGIT, LAG3. In samples from the same time points, we evaluated viral persistence, including residual viremia (by single copy assay; SCA), cell-associated RNA (CA-RNA), total HIV DNA (CA-DNA), and intact proviral DNA (IPD). Similarly, we assessed responses to HIV peptide pools (Gag, Pol, Env, Nef/Tat/Rev, Vif/Vpr/Vpu) and CMV/EBV by interferon gamma (IFNγ) ELISPOT.

**Results:** Participants (N=95) were on ART for a median of 6.8 years with median age of 48 (range 23-74) and a median CD4+ T cell count of 665 cells/$mm_3$. We observed nominally significant correlations between CA-DNA (N=89) and the frequency of CD4+ T cells expressing PD1/TIM3 (r=0.26; p=0.013, Spearman), PD1/PDL1/TIM3 (r=0.26; p=0.014), and TIM3 alone (0.31; p=0.004). CA-DNA also correlated with %CD8+ T cells expressing PD1/TIM3 (r=0.21; p=0.045) and PD1/PDL1/TIM3 (r=0.23; p=0.033). The correlations of the frequency of T cells expressing these IR combinations were not evident with CA-RNA, SCA, or IPD (IPD assay N=42). CD8+ T cell expression of combinations of PD1, PDL1, TIM3, and TIGIT was associated with IFNγ ELISPOT responses to Pol (r=0.23-0.27; p=0.021-0.046; N=73) and to Nef/Tat/Rev (r=0.23-26; p=0.029-0.046), but not to Gag and Env peptide pools. Frequencies of CD4+ T cells expressing IR combinations did not correlate with HIV-specific immune

responses. None of the combinations of IR expressed on the T cells were associated with CMV or EBV-specific responses.
**Conclusion:** After long-term suppressive ART, multiple IR expression on CD4+ and CD8+ T-cells is associated with greater persistence of HIV-infected cells and stronger IFNγ responses to specific HIV peptides. These seemingly contradictory findings suggest that persistent antigen expression from infected cells can stimulate both IFNγ and IR expression, the net effect of which is failure to clear HIV-infected cells. Determining whether expression of specific combinations of IR facilitates HIV persistence is a priority.

## 262 INVESTIGATING ANTIGEN-INDEPENDENT CD8+ T-CELL ENFORCEMENT OF HIV LATENCY

**Talia M. Mota**[1], Jared Weiler[1], Louise Leyre[1], Sandra Terry[1], Lynsay MacLaren Ehui[1], Avery Wimpelberg[2], Christopher M. Cannon[2], Sarah Henn[2], Erika Benko[3], Colin Kovacs[3], R. Brad Jones[1]
*[1]Weill Cornell Medicine, New York, NY, USA, [2]Whitman-Walker Health, Washington, DC, USA, [3]Maple Leaf Clinic, Toronto, Canada*

**Background:** Recent research supports the possibility that non-canonical behaviors of CD8+ T-cells can reduce HIV expression in infected cells in an antigen-independent noncytolytic manner, paralleling observations from other pathogenic infections. We aimed to confirm this 'innate-like' behavior in CD8+ T-cells using a precise antigen-independent experimental system by 1) abrogating surface expression of MHC Class I so that HIV-infected CD4+ T-cells cannot present antigen to HIV-specific CD8+ T-cells, and by 2) ruling out common death-receptor pathways of CD8+ T-cell mediated killing that may otherwise function without MHC I recognition.
**Methods:** To investigate the antigen-independent impact of primary CD8+ T-cells on HIV expression in CD4+ T-cells, we first established a system to abrogate surface expression of MHC I (HLA-A/B/C/E) using CRISPR/Cas9 and two guide RNAs against beta-2-microglobulin (ß2M). MHC I KO was performed in HIV-JRCSF-infected CD4+ T-cells from people with HIV and exposed overnight to autologous primary unstimulated or TCR-stimulated CD8+ T-cells (n=6), including CD8+ T-cells with CRISPR KO of cytotoxic granules including Perforin, Granzyme A and B, the TCR, and death receptor ligands including FasL, TRAIL, and NKG2D (n=2).
**Results:** CRISPR/Cas9 targeting ß2M abrogated MHC I surface expression in up to 98% of cells within 48hrs. In HIV-JRCSF-infected CD4+ T-cells, co-culture with unstimulated primary CD8+ T-cells resulted in a median of 5% reductions in Gag+ cells within the MHC-Ipos cells (not significant), while co-culture with anti-CD3/28-stimulated CD8+ T-cells drove a 29% reduction (Friedman test; $p<0.01$). In MHC-Ineg cells (which cannot present antigens to CTLs), medians of 4% (ns) and 17% (Friedman test; $p<0.01$) reductions in the proportions of CD4+ T-cells expressing Gag were observed when exposed to unstimulated and TCR-stimulated CD8+ T-cells, respectively (Friedman test; $p<0.001$ for both). Although these studies are ongoing, thus far, knocking out cytotoxic effector molecules or death receptors/ligands did not impair this effect.
**Conclusion:** These results add to the evidence suggesting that a previously unrecognized CD8+ T-cell-mediated activity contributes to reductions in viral expression. This potential 'innate-like' behavior of primary CD8+ T-cells provides impetus to further study mechanisms to target these pathways with immunotherapeutics that may augment host cellular pathways to either enhance latency reversal or to improve viral suppression.

## 263 HLA-II–ASSOCIATED VIRAL ADAPTATION IMPACTS CD4+ T-CELL RESPONSES IN HIV-1 VACCINES

New Investigator Scholar

**Jacob K. Files**[1], Sarah Sterrett[1], Timothy Fram[1], Nathan Erdmann[1], Anju Bansal[1], Paul Goepfert[1]
*[1]University of Alabama at Birmingham, Birmingham, AL, USA*

**Background:** Human immunodeficiency virus-1 (HIV-1) has been known to adapt to host CD8+ T-cell responses, negatively impacting disease progression. Our group has previously used HLA-II associated HIV viral polymorphisms to predict CD4 T-cell escape in HIV infected individuals. In the current study we assess whether HLA-II associated viral adaptation adversely impacts vaccine-induced CD4+ T-cell responses in HIV-1 vaccine recipients.
**Methods:** We designed vaccine-matched epitopes containing evidence of adaptation (adapted epitopes or AE) and epitopes having no evidence of adaptation (non-adapted epitopes or NAE). PBMC samples were obtained from three different HIV-1 vaccine trials including MRKAd5 (Step Study or HVTN 502; n=20), DNA/rAd5 (HVTN 505; n=20) and DNA/MVA (HVTN 106; n=30). To determine differences in immunogenicity, we utilized a combination of CD8-depleted IFNγ ELISpot assays, flow cytometric activation induced marker (AIM) assays, and single-cell RNA sequencing assays.
**Results:** Vaccine-encoded AE induce lower magnitude CD4+ T-cell responses in comparison to NAE based on CD8-depleted ELISpot and activation induced marker (AIM) assays. These results were confirmed in a single mosaic vaccine recipient, where we saw that CD4+ T-cell responses to an encoded AE were dampened in comparison to the corresponding encoded NAE. While there were no differences in the effector/memory sub-populations between these two antigen-specific CD4+ T-cell populations, AE-specific CD4+ T-cells from DNA/rAd5 vaccinees exhibited a lower frequency of cells with a peripheral T-follicular helper (pTfh) phenotype. Single-cell transcriptomic analyses show that NAE-specific CD4+ T-cells demonstrated increased gene expression of IFNγ, TNFα, and IL21, suggestive of a Th1 or Tfh phenotype, whereas AE-specific CD4+ T-cells have increased IL13 and IL17f, suggestive of a Th2 or Th17 phenotype.
**Conclusion:** Together, these findings show that HLA-II adaptation negatively impacts quantity and skew the quality of CD4+ T-cell responses in HIV-1 vaccine recipients and suggests that future HIV-1 vaccine design may improve CD4+ T-cell responses by considering HLA-II viral adaptation.

## 264 TFH-SPECIFIC FEATURES ASSOCIATED WITH NEUTRALIZATION IN CHRONIC HIV-1 INFECTION

**Eirini Moysi**[1], Ashish A. Sharma[2], Sijy O'Dell[1], Clarisa Buckner[1], Perla Mariana Del Rio Estrada[3], Gustavo Reyes-Teran[3], Alexander J. Chassiakos[1], Margaret H. Beddall[1], Nicole Doria-Rose[1], Susan Moir[1], Rafick-Pierre Sékaly[1], John R. Mascola[1], Richard A. Koup[1], Constantinos Petrovas[1]
*[1]National Institutes of Health, Bethesda, MD, USA, [2]Emory University, Atlanta, GA, USA, [3]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico*

**Background:** Follicular helper T —cells (TFH) are critical for the development of neutralizing antibodies following infection and vaccination. During HIV—1 disease, TFH accumulate in the germinal centers (GC) of lymphoid tissues possibly due to immune activation. Despite this accumulation, only a small percentage of HIV—infected individuals are able to mount a broadly neutralizing response. The drivers of this discrepancy at tissue level remain to be elucidated. We therefore performed a detailed analysis of the immunophenotype, topology and transcriptional signatures of TFH in viremic HIV+ donors with and without evidence of serum neutralizing activity.
**Methods:** LN cell suspensions and matched formalin—fixed, paraffin embedded tissues were analyzed using 30—parameter flow cytometry, quantitative multiplexed confocal imaging and single—cell RNA analysis using the 10x genomics 3´ scRNA—seq kit. Neutralization activity of matched serum samples was determined using a single—round—of—infection Env—pseudotyped virus assay. We classified donors into two groups; non-neutralizers had serum ID50 > 40 for ≤1/20 pseudoviruses, while neutralizers had serum ID50 > 40 for at least 6/20 pseudoviruses
**Results:** Flow cytometric analysis revealed significantly higher frequencies of CD4+ T—cells with a central memory phenotype (CD27hi/loCD45ROhi) in HIV+ neutralizers compared with non—neutralizers ($p=0.026$) and a concomitant trend for increased TFH (CXCR5hi PD-1hi) in LMNC suspensions and in—situ (CD4hi PD-1hi within CD20hi/dim follicular areas). Higher frequencies of activated (CD95+) ICOS+ and CD57+ expressing TFH were also observed in neutralizers consistent with an increased capacity for optimal T-cell help ($p=0.0365$). Furthermore, using an unsupervised scRNAseq analysis approach, we observed distinct clustering between non—neutralizer and neutralizer TFH cells driven by 40 differentially expressed genes. Compared to non—neutralizers, neutralizer cells expressed higher levels of FKBP5, IL6ST, CAV-1, IKZF4, GNG4, TRIM8, MYCBP2, TCF7, LIMS1 and FYB1, with associated pathways and TCF7 in particular implying increased potential for self-renewal and differentiation.
**Conclusion:** Our results suggest distinct phenotypic and transcriptional TFH signatures in the lymph nodes of untreated, chronically HIV-infected individuals with and without neutralizing antibodies which could have implications for the development of future vaccine strategies.

## 265 HIV-SPECIFIC T-CELL FREQUENCIES AND FUNCTION AFTER ART DURING ACUTE OR EARLY HIV

**Scott F. Sieg**[1], Joseph A. Puleo[2], Lu Zheng[2], Brian Clagett[1], Javier R. Lama[3], Lawrence Fox[4], Jintanat Ananworanich[5], Kiat Ruxrungtham[6], Beatriz Grinsztejn[7], Roberto C. Arduino[8], Joseph J. Eron[9], John W. Mellors[10], Eric S. Daar[11], Trevor A. Crowell[12]

[1]Case Western Reserve University, Cleveland, OH, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Asociacion Civil Impacta Salud y Educacion, Lima, Peru, [4]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [5]University of Amsterdam, Amsterdam, Netherlands, [6]Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [7]Institute de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil, [8]The University of Texas Health Science Center at Houston, Houston, TX, USA, [9]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [10]University of Pittsburgh, Pittsburgh, PA, USA, [11]Harbor–University of California Los Angeles Medical Center, Torrance, CA, USA, [12]Walter Reed Army Institute of Research, Silver Spring, MD, USA

**Background:** Antiretroviral therapy (ART) started during acute or early HIV infection (AEHI) has multiple benefits, but its immunologic effects are not well defined. We hypothesized that early ART would limit antigen exposure and reduce T cell immune responses in a multinational, prospective, open-label study of early ART.

**Methods:** ACTG A5354 enrolled and rapidly initiated ART in adults with Fiebig stages I-V of AEHI at 30 sites in the Americas, Africa and Southeast Asia. Fiebig stage at start of ART was assigned retrospectively by centralized testing. A secondary endpoint of A5354 was to assess if timing of ART during AEHI influenced HIV-specific T cells after 48 weeks of ART. Comparisons were between pre-specified study Groups; Group 1 (G1) Fiebig I/II (n=49); Group 2 (G2) Fiebig III/IV (n=79); and Group 3 (G3) Fiebig V (n=60). Peripheral blood mononuclear cells were stimulated (6 h) with PTE peptide pools (NIH HIV Reagent Program) consisting of env, gag, nef, or pol peptides, SEB (positive control) or incubated without stimulation (negative control). Brefeldin A and CD107a antibody (for staining) were added during the 6 h incubation. Cells were stained for expression of CD3, CD4 and CD8 and intracellular CD40L, Mip1b, IFN-g and TNF-a and analyzed by flow cytometry excluding debris, doublets and dead. HIV DNA copies/million CD4 T cells was determined by qPCR.

**Results:** Frequencies of T cells that expressed any one of the possible activation markers were diminished in G1 participants compared to other groups (Figure). Significant differences (Wilcoxon Test; $p<0.05$) were observed for gag- and pol-specific CD8+ and CD4 + T cell responses (G1 vs G2) as well as for nef-specific CD8+ T cells responses (G1 vs G3 and G2 vs G3). T cell polyfunction among cells expressing activation markers was similar across groups; modest, but significant ($p<0.05$) differences, were noted comparing G1 vs G2 for percentages of HIV-reactive CD4+ T cells expressing two functions after stimulation with env (median: 11.2 vs 9.0), nef (10.1 vs 8.8) or pol (10.7 vs 8.7). Frequencies of HIV-specific T cells were not correlated with total HIV DNA ($|\text{Spearman r}| \leq 0.15$, $p>0.07$; unadjusted and adjusted for study groups) at week 48.

**Conclusion:** ART initiation in the earliest Fiebig stages (I/II) reduces frequencies but not polyfunction of HIV-specific T cells. Frequencies of HIV-infected cells that persist on ART do not appear to drive HIV-reactive T cells in adults treated during AEHI.

## 266 TREATMENT INTERRUPTION AND T-CELL IMMUNITY IN ART-TREATED PRIMARY HIV INFECTION

New Investigator Scholar

**Timothy L. Tipoe**[1], Ane T. Ogbe[1], Helen Brown[1], Nicola Robinson[1], Ming J. Lee[2], Rebecca Hall[3], Claire Petersen[3], Heather Lewis[3], John Thornhill[4], Julianne Lwanga[5], Fiona Ryan[5], Julie Fox[5], Sarah Fidler[2], John Frater[1]

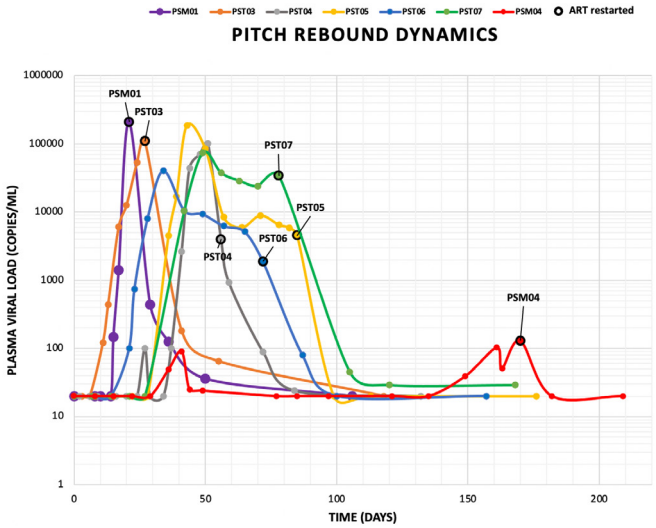
[1]University of Oxford, Oxford, UK, [2]Imperial College London, London, UK, [3]Imperial College Healthcare NHS Trust, London, UK, [4]Barts Health NHS Trust, London, UK, [5]Guy's and St Thomas' NHS Foundation Trust, London, UK

**Background:** Factors that predict post-treatment control (PTC) after stopping antiretroviral therapy remain undetermined. In animal models, HIV-specific T cell immunity has been associated with improved viral control following treatment interruption (TI). We conducted a prospective study of treatment interruption in primary HIV infection (PHI) to look for PTC and determine immune correlates of protection.

**Methods:** PITCH was a prospective open-label study of participants who initiated ART within an estimated 6 months of PHI with viral suppression (<50 copies HIV RNA/ml) for at least 2 years and HIV DNA levels ≤3.25 log copies/million CD4 cells. Participants underwent TI and were followed weekly. The decision to re-start ART was determined using a rule-based algorithm incorporating degree and duration of viraemia. T cell immunity to HIV antigens was assessed by IFNγ ELISpot; 200,000 cryopreserved PBMCs were stimulated with Gag, Pol, Acc, Env or Nef overlapping peptide pools. 50,000 cryopreserved PBMCs/well were used for positive controls PHA, and antigen-specific controls CMV and FECT. A total of 6 timepoints, before and after TI, were analysed for each participant and associations between immune responses and viraemia were determined by Spearman correlations.

**Results:** 11 participants were screened and 7 underwent TI. Of the 7 participants who agreed to take a TI, all rebounded and re-started ART achieving fully suppressed plasma viral loads. There were no major adverse events, including during the ATI. Time to rebound after TI ranged from 15 – 170 days (median 36 days) with 4 participants showing evidence of viral control for >30 days. 1 participant showed evidence of longer post-treatment control (170 days) with stepwise increases in Gag-specific responses after viral blips. There was heterogeneity in T cell responses following TI. With regards to immunodominance, participants tended to show dominant responses towards Gag, Env and Nef prior to TI. After ART resumption, all participants had dominant responses toward Gag and/or Pol. Only Env-specific responses were positively correlated with viral load ($r=0.44$, $p=0.0015$).

**Conclusion:** Treatment interruptions enhance and can cause changes in the immunodominance of host T cell responses. Further studies will resolve epitope-specific responses in the context of times to rebound.




## 267 PBMC TRANSCRIPTOME REVEALED A BENEFICIAL IMMUNE ACTIVATION AGAINST HIV-1 IN LGMD1F

New Investigator Scholar

**Francisco Diez-Fuertes**[1], Sara Rodríguez-Mora[1], Javier García-Pérez[1], Esther Calonge[1], Mercedes Bermejo[1], María Rosa López-Huertas[1], Mayte Coiras[1], José Alcamí[1]

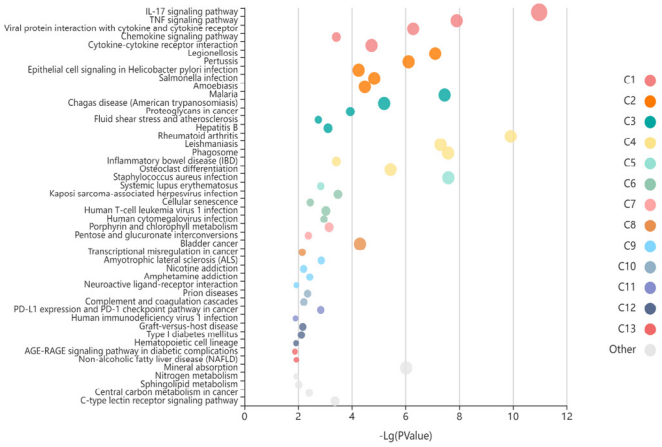
[1]Institute of Health Carlos III, Madrid, Spain

**Background:** TNPO3 is an importin involved in nuclear transport of splicing factors and HIV capsid. Limb-girdle muscular dystrophy (LGMD1F) is a rare genetic muscle disease characterized by a heterozygous deletion in TNPO3 gene, which generates an isoform with 15 additional amino acids. Our previous studies in 32 individuals affected by LGMD1F demonstrated that cells from these patients are resistant to HIV infection in vitro through interference with viral integration.

**Methods:** Peripheral blood mononuclear cells (PBMC) from 20 participants were isolated, including 10 individuals affected by LGMD1F and 10 non-affected relatives. Libraries were sequenced in a NextSeq550 platform (Illumina). Plasma levels of IFN-β and IFN-γ were measured by a Luminex assay (R&D Systems). Full-length HIV clone and VSV-pseudotyped infections were assessed in PBMC activated with CD3+CD28+IL2. Expression of MxA in infected lymphocytes was determined by flow cytometry

**Results:** A total of 545 differentially expressed (DE) genes were identified. Among the top 25 DE genes, we found an upregulation in LGMD1F patients of genes implicated in G protein-coupled receptor binding (CXCL1,3,5, and CCL7) and metalloendopeptidase activity (MMP1,8,10,12, S100A8, and S100A12). Functional annotation of DE genes denoted a pro-inflammatory response in LGMD1F patients as a result of the upregulation of 13 genes implicated in IL-17 signaling pathway ($p<10-8$) and 12 cytokines, including IL-1β, and metalloproteases associated with TNF signaling pathway ($p<10-6$; Fig.1). A dysregulation of 34 genes related to an exacerbated innate immune response

was also observed. In this sense, a 4.7- and 2.8-fold increase in plasma levels of IFN-β and IFN-γ, respectively, was detected in LGMD1F patients compared to controls ($p<0.05$). Moreover, PBMCs from LGMD1F patients infected ex vivo with VSV-pseudotyped virus and HIV-1 showed a 1.9- and 2.3-fold increase, respectively, in the expression of the IFN-stimulated gene MxA ($p<0.05$).
**Conclusion:** The present study gives a new perspective of LGMD1F pathology, providing new actors implicated in this muscular dystrophy, such as IL-17, metalloproteases, cytokines TNF and IL-1β, and the interferons. These findings suggest that TNPO3 mutation, either directly or through muscular damage, provokes changes in gene expression that increase basal immune activation in LGMD1F patients and confer an additive mechanism in restraining HIV-1 infection apart from the direct impact of TNPO3 in capsid transport and HIV integration.




## 268 ASSOCIATIONS BETWEEN MATRNAL HIV AND INFANT IMMUNE ACTIVATION

**Ceri Evans**[1], Bernard Chasekwa[2], Jonathan Broad[1], Christie Noble[1], Kuda Mutasa[2], Sandra Rukobo[2], Margaret Govha[2], Patience Mushayanembwa[2], Florence D. Majo[2], Naume V. Tavengwa[2], Jean H. Humphrey[3], Robert Ntozini[2], Claire D. Bourke[2], Andrew J. Prendergast[1]
*[1]Queen Mary University of London, London, UK, [2]Zvitambo Institute for Maternal and Child Health Research, Harare, Zimbabwe, [3]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*

**Background:** Children who are HIV-exposed but uninfected (CHEU) have more infectious morbidity and mortality than children who are HIV-unexposed (CHU), particularly in early life. We hypothesised that CHEU may have immunological abnormalities in infancy despite not living with HIV.
**Methods:** T-cell and monocyte immunophenotyping of fixed buffy-coat cells was undertaken by flow cytometry in a subgroup of participants of the SHINE trial in rural Zimbabwe. Proportions of T-cell and monocyte subsets, defined by surface and intracellular markers, were compared between CHEU and CHU aged 1-month using fractional regression, adjusted for infant sex and exact age in days.
**Results:** 146 CHEU and 142 CHU were included. 140/146 (96%) of CHEU were also antenatally-exposed to antiretroviral therapy (ART). Compared to CHU, a lower proportion of CD8+ T-cells in CHEU were naïve cells (CD45RA+/CD27+; mean 82.7% (standard deviation [SD] 22.0) vs. 90.0% (12.4), adjusted difference -7.4% [95%CI -13.0, -1.9], P=0.008), and higher proportions were central memory (CD45RA-/CD27+; +3.6% [0.6, 6.6], P=0.020) or effector memory (CD45RA-/CD27-; +2.1% [0.7, 3.5], P=0.003) cells. Higher proportions of CD8+ T-cells were proliferating (Ki67+; 15.2% (19.4) vs. 9.3% (11.5), +6.1% [1.7, 10.5], P=0.006) or co-expressing CD38 and HLA-DR activation makers (12.1% (16.5) vs. 6.4% (8.8), +4.3% [1.4, 7.2], P=0.003). There were no differences in CD4+ T-cell subsets. Compared to CHU, CHEU had higher concentrations of soluble CD14 (mean $1.10x10_6$ (SD 0.4) pg/mL vs. $0.85x10_6$ (0.4) pg/mL, adjusted difference $0.25x10_6$ [95%CI 0.15x106, 0.35x106], P<0.001) and lower proportions of classical monocytes (CD14+/CD16-; 57.5% (13.7) vs. 61.7% (15.5); -4.5% [-8.7, -0.2]; P=0.04). Monocyte population differences between CHEU and CHU were stronger in males compared to females, mostly driven by an expansion in non-classical (+6.2% [95%CI 0.0, 12.4]; P=0.05) rather than intermediate (-0.3% [95%CI -3.0, 0.2], P=0.84), monocytes.
**Conclusion:** Despite high maternal ART coverage, CHEU have a distinct cellular immune phenotype relative to CHU. Future work should explore associations between infant immunity and clinical outcomes. Strategies additional to antenatal ART may be required to improve outcomes amongst HIV-exposed children.

## 269 IMPACT OF ANTIMICROBIALS ON PENILE IMMUNOLOGY: A RANDOMIZED CLINICAL TRIAL

**Ronald Galiwango**[1], Brenda Okech[2], Vineet Joag[1], Sanja Huibner[1], Victoria M. Biribawa[2], Juliet Mpendo[2], Moses Muwanga[3], Daniel Park[4], Tony Pham[4], Cindy Liu[4], Aaron Tobian[5], Lane Buchanan[6], Jessica Prodger[6], Rupert Kaul[1]
*[1]University of Toronto, Toronto, Canada, [2]International AIDS Vaccine Initiative, Entebbe, Uganda, [3]E-Da Hospital, Kaohsiung City, Taiwan, [4]George Washington University, Washington, DC, USA, [5]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [6]Western University, London, Canada*

**Background:** The foreskin is the main site of HIV acquisition in heterosexual uncircumcised men. Preputial anaerobic bacteria enhance penile HIV susceptibility through increased inflammatory cytokines and local recruitment of HIV-susceptible CD4+ target cells. However, the penile immune effects of antimicrobial treatments are not defined. We performed a clinical trial to examine the impact of antimicrobials on ex vivo foreskin HIV susceptibility and preputial soluble immune factors.
**Methods:** This open label clinical trial randomized 125 HIV-uninfected, STI-free Ugandan men requesting voluntary penile circumcision (PC) to one of five arms (n=25 each). The control group received immediate PC, while four intervention groups deferred PC for 4 weeks and received either oral tinidazole for 2 days, or one of penile topical metronidazole, topical clindamycin or topical hydrogen peroxide twice daily for one week then biweekly until PC. The primary endpoint was ex vivo clade A HIV pseudovirus entry into foreskin-derived CD4+ T cells following PC. Secondary endpoints were: (1) safety and tolerability and (2) impact on 9 soluble immune factors in prepuce swabs at 1 and 4 weeks (multiplex ELISA).
**Results:** 125 participants were enrolled between 12/2017-11/2018, and 116 (93%) completed the protocol. The median participant age was 24 years (range, 18-49 years). All antimicrobial treatments were well tolerated. Oral tinidazole reduced HIV virus entry into foreskin-derived CD4+ T cells vs. controls (9.3% vs. 13.1%, p=0.017), with a trend to lower CCR5 expression (36.8% vs. 44.5%, p=0.09), but had no effect on soluble immune factors in the penile prepuce. Topical treatment had no impact on foreskin T cell subsets or virus entry, but all three treatments reduced preputial levels of soluble E-cadherin ($p<0.01$), suggesting improved epithelial integrity, and both clindamycin and metronidazole reduced the proinflammatory cytokine IL1b ($p<0.05$). Immunofluorescent staining of inner foreskin tissues confirmed that cellular adherens junctions were enhanced by topical antimicrobials ($p<0.05$), most strongly by topical metronidazole (p=0.035).
**Conclusion:** All antimicrobials studied in this pilot clinical trial had significant effects on penile immunology, with quite different effect patterns for oral vs. topical administration. In future work we hope to correlate inter-individual and inter-agent heterogeneity in immune outcomes with treatment-induced changes in the penile microbiome.

## 270 COCAINE AND PERIPHERAL SEROTONIN DRIVE IMPAIRED T-CELL FUNCTION AND HIV PERSISTENCE

**Mehul Sharma**[1], Maggie Fu[1], Xuan Xu[2], Daniela Schlatzer[2], Rebeka Bordi[3], Susan Pereira Ribeiro[3], Joumana Zeidan[3], Mark Chance[2], Marianna K. Baum[4], Rafick-Pierre Sékaly[3], Ashish A. Sharma[3]
*[1]University of British Columbia, Vancouver, Canada, [2]Case Western Reserve University, Cleveland, OH, USA, [3]Emory University, Atlanta, GA, USA, [4]Florida International University, Miami, FL, USA*

**Background:** Chronic cocaine users on complete anti-retroviral therapy (cART) are observed to have poor CD4 T cell reconstitution and HIV persistence which goes hand-in-hand with heightened pro-inflammatory responses. We hypothesized that pro-inflammatory responses downstream of cocaine use drive the maintenance of latent HIV.
**Methods:** Whole blood (plasma and mononuclear cells) was analyzed using an integrated multi-omic (metabolomics, transcriptomics, plasma cytokines, and flow cytometry) approach to uncover mechanisms that drive lower CD4 counts and higher inducible HIV levels in a cohort of cART treated HIV infected cocaine users. A rigorous three-pronged approach (combination of questionnaire, urine test, and plasma mass-spectrometry based cocaine metabolite detection) was

used to determine cocaine use status and 17 (of 36) subjects were defined as users.

**Results:** These subjects had significantly higher levels of plasma pro-inflammatory cytokines (TNF-a, IL-10 and decreased TGF-b1; $p<0.05$) and serotonin ($p<0.01$) in peripheral blood. Gene set enrichment analyses of whole blood transcriptome revealed that effector CD8 T cell responses (Type II interferon signaling, IL2/STAT5 signaling) were positively enriched in cocaine users. Mediation analyses revealed an intermediary role of peripheral serotonin in driving these effector responses. In vitro exposure of purified T cells to a wide range of serotonin concentrations resulted in the upregulation of co-inhibitory receptors (PD1, LAG3), impaired proliferation (decreased Ki67) and lower frequencies of polyfunctional T cells (decreased TNF-a and IL-2; $p<0.05$, 2x-lower MFI). The activated/exhausted state of T-cells in cocaine users was confirmed ex vivo by an observed decrease in surface protein levels of BTLA/CD150 on CD8+ T-cells and increased frequency of CTLA4+ PD1+ CD4+ T-cells i.e. effector Tregs. Importantly, we observed that levels of inducible HIV (TILDA) ex vivo positively correlated with plasma TNF-a and negatively with serotonin ($p<0.001$, rho=0.7277).

**Conclusion:** Our findings show that over-activated immune profile in HIV-infected cART-treated cocaine users drives poor CD4 proliferation and higher inducible HIV. The mechanisms uncovered here can prove to be crucial for the design of medical interventions aimed at restoring CD4 T cell numbers and lowering latent HIV reservoirs in cART-treated chronic cocaine users.

### 271 LOSS OF TOLERANCE AND ANERGY IN HUMAN PERIPHERAL B CELLS DURING SARS-CoV-2 INFECTION

**Moriah J. Castleman**[1], Megan Stumpf[1], Nicholas Therrien[1], Brenda Martinez[1], Roberta Pelanda[1], Raul Torres[1]

*[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** Severe infection with SARS-CoV-2 induces systemic autoreactive antibodies with specificity to Type I IFN, phospholipids, nuclear or tissue specific targets. The wide breadth of targets suggests a system-wide defect in B cell tolerance during viral infection and that the source of autoreactive antibodies is likely a heterogenous subset of B cells. BND cells are mature naïve B cells that do not express IgM but do express IgD and are enriched in autoreactive specificities. BND cells are held in an anergic state in healthy humans as a mechanism of peripheral tolerance, although in vitro evidence suggests anergy can be broken with strong inflammation. We hypothesized that robust inflammation associated with viral infection from SARS-CoV2 may relax peripheral tolerance and promote breakage of BND cell anergy.

**Methods:** Plasma and PBMCs were collected from healthy controls (N=10), subjects immunized with Pfizer BNT162b2-mRNA/ Moderna mRNA-1273 (N=10), subjects with mild (N=11) or severe SARS-CoV-2 infection (N=14). BND cells were examined ex vivo for markers of activation by flow cytometry. Phosphorylation of signaling proteins downstream of the BCR were measured in vitro with or without BCR crosslinking. Inflammatory cytokines were measured in plasma by multiplex. For statistical analysis, unpaired t test between populations or paired t test between unstimulated and BCR stimulated conditions were performed.

**Results:** BND cells from severe SARS-CoV-2 infection have lower expression of CD21, associated with loss of anergy, higher expression of activation markers CD68 and CD86 with lower expression of inhibitory receptors CD22 and CD72 when compared to BND cells from other subjects, suggesting a phenotypical breach of anergy. Upon BCR crosslinking, BND cells have higher levels of downstream signaling components of the BCR (pPLCγ2, pBlnk, and pSyk) when compared to healthy controls and immunized subjects, suggesting a functional breach in anergy with infection. Examination of plasma from severe SARS-CoV-2 infection showed higher levels of inflammatory cytokines (IFNγ, TNFα, IL-6 and CRP) where TNFα and CRP correlated with enhanced BCR signaling in BND cells.

**Conclusion:** We demonstrate that SARS-CoV-2 viral infection relaxes peripheral tolerance of BND cells, likely through strong systemic inflammation produced during infection. These autoreactive cells overcome anergy and become activated with increased BCR signaling. Thus BND cells could be a source of autoreactive antibodies during viral infection.

### 272 STRAIN-SPECIFIC SEROLOGICAL RESPONSE FOLLOWING SARS-CoV-2 VOC INFECTION

**Karlijn van der Straten**[1], Denise Guerra[1], Meliawati Poniman[1], Dirk Eggink[2], Marloes Grobben[1], Chantal Reusken[2], Hugo D. van Willigen[3], Elke Wynberg[4], Menno D. de Jong[1], Maria Prins[4], Tim Beaumont[1], Godelieve De Bree[3], Rogier W. Sanders[3], Marit J. van Gils[3]

*[1]Amsterdam University Medical Center, Amsterdam, Netherlands, [2]National Institute for Public Health and the Environment, Bilthoven, Netherlands, [3]Academic Medical Center, Amsterdam, Netherlands, [4]Public Health Service Amsterdam, Amsterdam, Netherlands*

**Background:** The emergence of new SARS-CoV-2 variants raises concerns whether preexisting artificial (vaccine-induced) and natural immunity from prior COVID-19 prevents re-infections. Here, we investigated the differences in primary humoral immune response following SARS-CoV-2 variants of concern (VOCs) infection and aimed to identify the key mutations involved in these differences.

**Methods:** Patients with primary PCR-proven SARS-CoV-2 infection with no history of previous COVID-19 vaccination were included between October 2020 and May 2021 at Amsterdam UMC and via the Dutch SARS-CoV-2 sequence surveillance program. Serum was collected 4-8 weeks after symptom onset and tested for IgG binding and pseudovirus neutralization of the wild-type (WT, Wuhan/D614G), Alpha, Beta and Delta variants.

**Results:** We included 51 COVID-19 patients, who were infected with the WT (n=20), Alpha (n=10), Beta (n=9) or Delta variant (n=12). Generally, the highest neutralization titers were against the autologous virus. After stratifying for hospitalization status, non-hospitalized patients infected with the WT (ID50 817) or Alpha (ID50 2524) variant showed the strongest geometric mean autologous neutralization, followed by the Delta variant (ID50 704) infected participants. By contrast, only one participant infected with the Beta variant showed strong autologous neutralization (median ID50 171). The VOCs also differed in their ability to induce cross-neutralizing responses, with WT-infected patients showing the broadest immune response, followed by Alpha, Delta and Beta infected participants. Additionally, participants infected with the WT, Alpha or Delta variant showed the lowest cross-neutralization against the Beta variant, with a median 5.0-fold (2 to 16-fold), 7.7-fold (2 to 32-fold), and 5.3-fold (1 to 19-fold) reduction compared to the autologous neutralization, respectively. We identified the E484K mutation as the key mutation responsible for this low cross-neutralization.

**Conclusion:** We demonstrated that even small differences in the S protein influences the polyclonal antibody response following infection. The low level of (cross-)neutralization induced by the Beta variant may implicate a higher re-infection risk, but further research of the memory B cell compartment and clinical studies are needed. The broadest cross-neutralizing response observed for WT-infected patients suggests that artificial immunity induced by the current approved COVID-19 vaccines already protects against many re-infections.

### 273 SARS-CoV-2 NEUTRALIZING RESPONSE BEYOND 1 YEAR AFTER INFECTION

**Benjamin Trinité**[1], Edwards Pradenas[1], Victor Urrea[1], Silvia Marfil[1], Ferran Tarrés-Freixas[1], Raquel Ortiz[1], Carla Rovirosa1, Jorge Carrillo[1], Roger Paredes[2], Anna Chamorro[2], Ruth Toledo[2], Marta Massanella[1], Bonaventura Clotet[1], Julià Blanco[1]

*[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Fight against AIDS Foundation (FLS), Germans Trias i Pujol Hospital, Badalona, Spain*

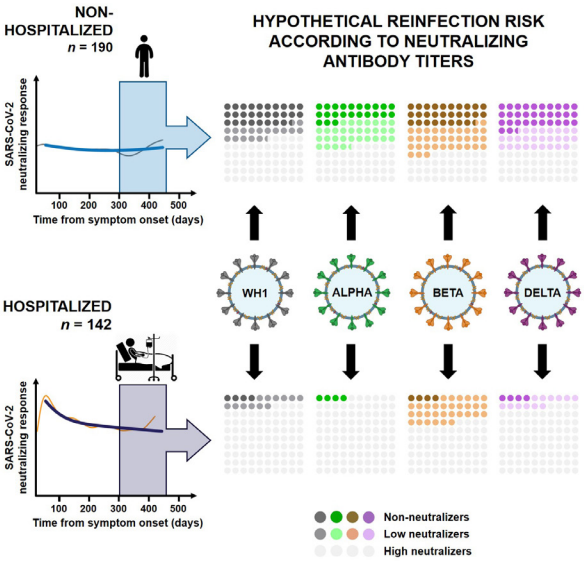
**Background:** Understanding the determinants of long-term immune responses to SARS-CoV-2 and the concurrent impact of vaccination and emerging variants of concern will guide optimal strategies to achieve global protection against the COVID-19 pandemic.

**Methods:** A prospective cohort of 332 COVID 19 patients was followed beyond one year. Plasma neutralizing activity was evaluated using HIV-based reporter pseudoviruses expressing different SARS-CoV-2 spikes and was longitudinally analyzed using mixed-effects models.

**Results:** Long-term neutralizing activity was stable beyond one year after infection in mild/asymptomatic and hospitalized participants. However, longitudinal models suggest that hospitalized individuals generate both short- and long-lived memory B cells, while responses of non-hospitalized were dominated by long-lived B cells. In both groups, vaccination boosted responses to natural infection. In unvaccinated participants, viral variants, mainly beta, reduced the efficacy of long-term (>300 days from infection) neutralization. Importantly, despite showing higher neutralization titers, hospitalized patients showed lower cross-neutralization of beta variant compared to non-hospitalized. Multivariate analysis identified severity of primary infection as

the factor that independently determines both the magnitude and the inferior cross-neutralization activity of long-term neutralizing responses.

**Conclusion:** Neutralizing response induced by SARS-CoV-2 is heterogeneous in magnitude but stable beyond one year after infection. Vaccination boosts these long-lasting natural neutralizing responses and should help counteract the resistance to neutralization of variants of concern such as the beta variant. Severity of primary infection determines higher magnitude but poorer quality of long-term neutralizing responses.




## 274 ESTABLISHMENT OF AN ANTI-RBD THRESHOLD THAT PREDICTS ROBUST NEUTRALIZING ACTIVITY

New Investigator Scholar

**Grace Kenny**[1], Sophie O'Reilly[1], Riya Negi[1], Alejandro A. Garcia[1], Obada Yousif[1], John S. Lambert[1], Aoife G. Cotter[1], Eoghan De Barra[2], Eoin Feeney[1], Peter Doran[1], Virginie W. Gautier[1], Patrick Mallon[1]

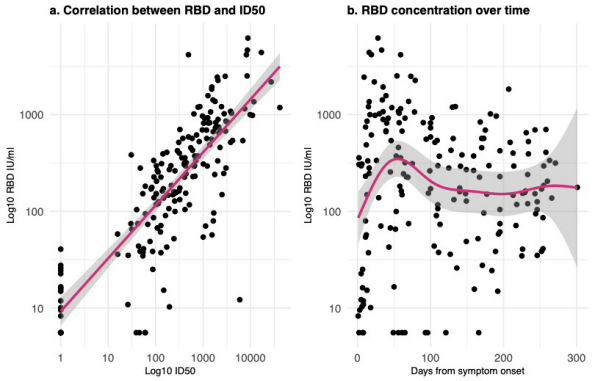
*[1]University College Dublin, Dublin, Ireland, [2]Royal College of Surgeons in Ireland, Dublin, Ireland*

**Background:** Although presence of SARS-CoV-2 neutralising antibodies can provide protection against development of COVID-19, how reflective circulating anti-SARS-CoV-2 antibody levels are of underlying neutralising capacity, and whether a threshold exists to predict sufficient neutralising capacity remains unclear.

**Methods:** In plasma from individuals with PCR-confirmed COVID-19 recruited to the All Ireland Infectious Diseases Cohort Study, we measured IgG concentrations against RBD, Spike protein sub-unit 1 and 2 (S1, S2) and Nucleocapsid (NC) using multiplex electrochemiluminescence (normalised to World Health Organisation reference serum as IU/mL). Neutralising capacity was measured against live SARS-CoV-2 virus (clinical isolate 2019-nCoV/Italy-INMI1) by determining the maximum plasma dilution required to maintain 50% inhibition of infection of Vero E6 cells (50% Neutralisation Titre (NT50)), by flow cytometry-based micro-neutralisation assay. Given that the Beta SARS-CoV-2 variant of concern (VOC) reduces neutralising activity up to six fold, we estimated a NT50 of 1:1000 against wild type SARS-CoV-2 would maintain neutralising activity against VOC. We used Spearman correlation and linear regression to model relationships between NT50 and IgG concentrations. Data are presented as median (IQR) unless specified.

**Results:** In 190 individuals (age 50 (40 - 64) years, 55% female, time from symptom onset 98 (35 - 179) days), NT50 most highly correlated with anti-RBD IgG (Rho 0.81 p<0.001, Fig 1a) compared with other IgG classes (S1; Rho 0.8, S2; 0.73, NC; 0.72, all p<0.001). Median RBD titre was 246 (71-662) but trended lower over time, with a median of 319 (61-1012) IU/ml at 0-90 days, 244 (86-523) IU/ml at 90-180 days and 157 (80-364) IU/ml at >180 days post symptom onset respectively (p=0.08, Fig 1b). RBD IgG titres of 476 IU/ml corresponded to a NT50 of 1:1000. Overall, RBD ≥476 IU/ml predicted NT50 ≥1:1000 with a sensitivity of 77 (95% CI 65-87)% and specificity 89 (95% CI 82-93)%. This improved in an analysis restricted to convalescent samples (>30 days post symptom onset, n=148), with a sensitivity 88% (95% CI 74-96%) and specificity 90% (95%CI 82-95%) respectively.

**Conclusion:** In convalescent plasma, RBD IgG titres ≥476IU/mL is sensitive and specific for predicting robust underlying neutralising capacity. Further research is required to validate these findings in other cohorts and confirm these thresholds in post-vaccinated individuals.




## 275 HIGHER CORONAVIRUS ANTIBODY RESPONSES PREPANDEMIC IN AFRICA THAN IN THAILAND

**Yifan Li**[1], Mélanie Merbah[1], Bradley Beckman[1], Thembi Mdluli[1], Heather Liu[1], Nittaya Phanuphak[2], Jonah Maswai[3], John Owuoth[4], Hannah Kibuuka[5], Michael Iroezindu[6], Emmanuel Bahemana[7], Sandhya Vasan[1], Julie Ake[1], Kayvon Modjarrad[8], Morgane Rolland[1]

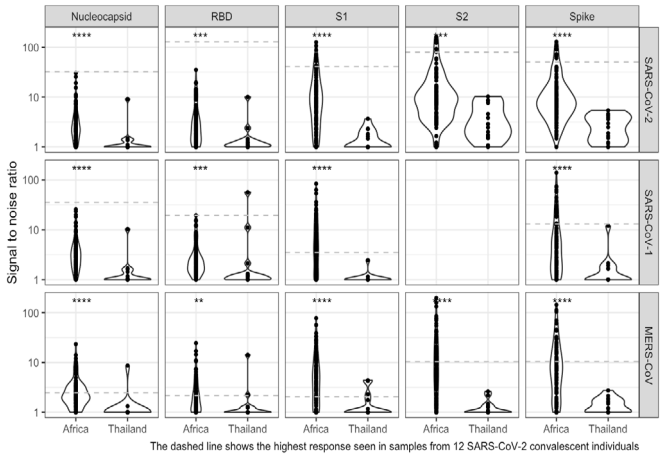
*[1]US Military HIV Research Program, Silver Spring, MD, USA, [2]SEARCH, Institute of HIV Research and Innovation, Bangkok, Thailand, [3]MHRP/U.S. Army Medical Research Directorate - Africa, Kericho, Kenya, [4]U.S. Army Medical Research Directorate - Africa, Kisumu, Kenya, [5]Makerere University Walter Reed Project, Kampala, Uganda, [6]MHRP/HJF Medical Research International, Abuja, Nigeria, [7]MHRP/HJF Medical Research International, Mbeya, Tanzania, United Republic Of, [8]Emerging Infectious Disease Branch, Walter Reed Army Institute of Research, Silver Spring, MD, USA*

**Background:** COVID-19 clinical manifestations range from asymptomatic to severe disease. Prior immune responses to human coronaviruses may affect individual responses to SARS-CoV-2. We surveyed coronavirus responses pre-pandemic in individuals from Kenya, Nigeria, Tanzania, Uganda and Thailand; 81% were people living with HIV.

**Methods:** Specimens were screened for SARS-CoV-2 Spike S2 subunit IgG responses. Selected samples were tested using a bead-based immunoassay that profiled the specificity, isotype and subclass of antibody responses to coronavirus, flavivirus and HIV antigens. Wilcoxon rank sum tests were performed to compare responses across antigens and participant group.

**Results:** We screened 1,875 samples (one per individual) collected between 2013 and October 2019: 1,630 samples were from Africa (87%) and 245 from Thailand. 6.99% of participants (n=131, 116 from Africa (89%) and 15 from Thailand) showed responses above the naïve signal threshold and were further tested. Using a signal to noise ratio of >10 as a cut-off value, 44, 27 and 42 samples showed IgG responses to the Spike protein of SARS-CoV-2, SARS-CoV-1 and MERS-CoV respectively, while 7, 9 and 4 samples showed responses to Nucleocapsid for these same antigens. Some individuals had higher responses than those seen in SARS-CoV-2 convalescent individuals. We found a strikingly different pattern of reactivity in Africa compared to Thailand (Figure 1). Antibody responses were significantly higher in the African participants compared to Thai participants across antigens corresponding to SARS-CoV-2 (p<0.001), SARS-CoV-1 (p<0.001) and MERS-CoV (p<0.01). Similar patterns were seen for IgG subclasses, IgA and IgM. The difference was less pronounced for the four endemic coronaviruses, nonetheless anti-Spike responses were significantly higher in African participants for HKU1 and OC43 (p≤0.018). In addition, mapping responses to 21 flavivirus antigens showed the highest reactivity in Thailand and in Nigeria.

**Conclusion:** Our serosurvey of pre-pandemic samples showed that there were significantly higher antibody responses against coronaviruses, including SARS-CoV-2, in Africa than in Thailand. Profiling flavivirus responses showed that the difference between the two regions was not due to a higher background reactivity across African samples. Further analysis is needed to explain pre-pandemic SARS-CoV-2-like antibody responses among African participants and explore implications for geographic diversity in disease severity.




## 276 PERSISTENCE OF SARS-CoV-2 ANTIBODIES IN CHILDREN AND ADULTS 1 YEAR AFTER INFECTION

**Costanza Di Chiara**[1], Anna Cantarutti[2], Paola Costenaro[1], Chiara Cosma[1], Bonfante Francesco[3], Sandra Cozzani[1], Maria Raffaella Petrara[1], Francesco Carmona[4], Cecilia Liberati[1], Paolo Palma[5], Anita De Rossi[1], Mario Plebani[1], Carlo Giaquinto[1], Andrea Padoan[1], Daniele Donà[1]

*[1]University of Padova, Padova, Italy, [2]University of Milano–Bicocca, Milan, Italy, [3]Istituto Zooprofilattico Sperimentale delle Venezie, Padua, Italy, [4]Istituto Oncologico Veneto, Padua, Italy, [5]Bambino Gesu Children's Hospital, Rome, Italy*

**Background:** Understanding the long-term kinetics of the immune response against SARS-CoV-2 infection is crucial in guiding public health policies and optimizing of vaccination strategies. While it is known that SARS-CoV-2 specific antibodies may persist in adults 12 months after infection, data are lacking in the pediatric population. We herein describe the long-term immune response in children following SARS-CoV-2 infection.

**Methods:** Single-centre, prospective observational study analyzing family clusters of COVID-19 attending the Pediatric Department, University of Padua (Italy). Confirmed COVID-19 infection was defined by positive SARS-CoV-2 PCR and/or IgG serology. All patients with confirmed infection at enrolment underwent serological follow-up at 1-4, 5-10, and >10 months after infection. Plasma was analyzed to quantify anti-SARS-CoV-2 S-RBD IgG, by chemiluminescent immunoassay, performed on MAGLUMI™2000 Plus (Snibe Diagnostics). IgG title >4.3 kBAU/L was considered positive.

**Results:** Among 902 subjects (252 COVID-19 family clusters), 698 had confirmed COVID-19, including 352 children/older siblings aged 8.6 ±5.1 years, and 346 parents aged 42.5 ±7.1 years; of those, 96.5% cases had asymptomatic/mild COVID-19. Children showed significantly higher S-RBD IgG titers than older subjects across all follow-up time points, with an overall mean S-RBD IgG titer <3 years of age five-fold higher than adults (282.3 [139-516.6] kBAU/L vs 56.7 [24.6-136.9] kBAU/L, p<0.001) (Table). The longitudinal analysis of 60 subjects sampled at least twice during follow-up demonstrated the persistence of antibodies up to 10 months from infection in all age classes. Subjects >6 years of age showed a significant progressive decline of the S-RBD IgG titer from the first serological follow-up. While, in younger children antibodies remained stable at 5-10 months of follow-up (p=0.0625), with a subsequent significant decline afterwards (p<0.001).

**Conclusion:** In our unique family cluster cohort, we confirmed the different kinetics of the COVID-19 humoral response across several age groups of asymptomatic/mild COVID-19 cases in our family-cluster cohort. Children presented with higher S-RBD IgG titer at every time point up to 10 months of follow-up. Children less than 3 years demonstrated a more intense long-term resilience of their immune response, which started to decline significantly only after ten months from infection.

**All data, irrespective of onset**

| Age Classes (yr.) | < 3 yr. (n=69) | 3 ≤ yr. < 6 (n=65) | 6 ≤ yr. < 12 (n=158) | 12 ≤ yr. < 18 (n=114) | ≥ 18 yr. (n=381) | p-value‡ |
|---|---|---|---|---|---|---|
| | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) | |
| S-RBD IgG (kBAU/L) | 282.3 (139 - 516.6) | 168.9 (101.8 - 265.9) | 126.2 (72.3 - 207.8) | 98.5 (44.8 - 169) | 56.7 (24.6 - 136.9) | <0.0001 |

**At 1 - 4 months, from onset**

| Age Classes (yr.) | < 3 yr. (n=49) | 3 ≤ yr. < 6 (n=36) | 6 ≤ yr. < 12 (n=109) | 12 ≤ yr. < 18 (n=74) | ≥ 18 yr. (n=262) | p-value‡ |
|---|---|---|---|---|---|---|
| | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) | |
| S-RBD IgG (kBAU/L) | 340.1 (161.9 - 519.6) | 234.6 (113.5 - 347.9) | 164.1 (79.1 - 236) | 103.1 (46.3 - 170.2) | 64.5 (26.2 - 140.9) | <0.0001 |

**At 5 - 9 months, from onset**

| Age Classes (yr.) | < 3 yr. (n=10) | 3 ≤ yr. < 6 (n=19) | 6 ≤ yr. < 12 (n=33) | 12 ≤ yr. < 18 (n=25) | ≥ 18 yr. (n=79) | p-value‡ |
|---|---|---|---|---|---|---|
| | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) | |
| S-RBD IgG (kBAU/L) | 284.3 (162.5 - 519.6) | 118.2 (70.6 - 192.5) | 119.5 (72.3 - 160.2) | 93.5 (47.6 - 158.9) | 52 (22.5 - 126.4) | <0.0001 |

**≥ 10 months, from onset**

| Age Classes (yr.) | < 3 yr. (n=10) | 3 ≤ yr. < 6 (n=10) | 6 ≤ yr. < 12 (n=16) | 12 ≤ yr. < 18 (n=15) | ≥ 18 yr. (n=40) | p-value‡ |
|---|---|---|---|---|---|---|
| | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) | |
| S-RBD IgG (kBAU/L) | 146.5 (62.8 - 231.2) | 111.3 (47.6 - 160.6) | 91.4 (63 - 112.8) | 61.7 (18.2 - 136) | 37.1 (16.4 - 119.1) | 0,0263 |

## 277 IMMUNOAGONIST CONVERTS CMV-SPECIFIC T CELLS INTO MORE POTENT HIV-SPECIFIC CAR-T CELLS

New Investigator Scholar

**Hang Su**[1], Christopher Hiner[1], Moriah Rabin[1], Danica Lee[1], Stephanie Sabido[1], Scott J. Garforth[1], Jianhua Zheng[1], Kim Anthony-Gonda[2], Boro Dropulić[2], Steven C. Almo[1], Harris Goldstein[1]

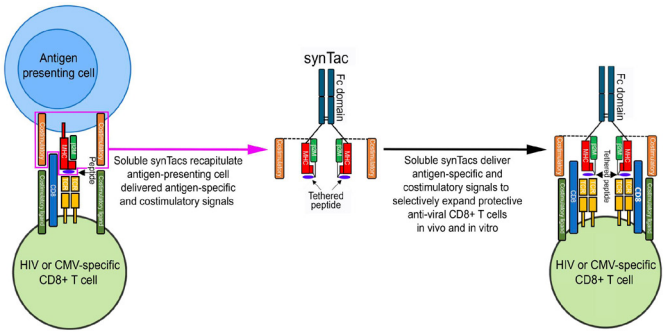
*[1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]Caring Cross, Gaithersburg, MD, USA*

**Background:** We developed novel immunoagonists (synTacs) to selectively activate and expand virus-specific CD8+ T cells in vitro and in vivo. SynTacs consist of dimeric Fc-domain scaffolds linking CD28-specific agonists to HLA-A2 MHC molecules covalently-tethered to a virus-derived peptide enabling delivery of TCR-specific and costimulatory signals to antigen-specific T cells. We hypothesized that synTac-activation of virus-specific effector-memory CD8+ T cells would selectively target them for lentiviral transduction, enabling generation of CAR-T cells with more potent and sustained activity than those produced by standard αCD3/αCD28 antibody (αCD3/28) activation. Using a duoCAR construct which targets two distinct HIV gp120 epitopes (HIV-CAR) to potently eliminate HIV-infected cells, we determined if selectively engineering HIV-CAR into CMV-specific memory CD8 T cells generated more potent HIV-CAR-T cells than those generated by standard αCD3/28 polyclonal T cell activation

**Methods:** CD8+ T cells purified from an HIV(-)/CMV(+) donor were activated by αCD3/28 or CMV-NLV-αCD28-synTac (CMV-synTac), a synTac linked to a CMV-pp65-peptide (NLVPMVATV) and CD28-specific agonist, and transduced with an HIV-CAR lentivector. HIV-CAR-T cells were either cocultured or co-injected into NSG mice with HIV luciferase-infected autologous PBMCs to measure in vitro and in vivo viral suppression

**Results:** Ten days after CMV-synTac treatment, CMV-specific CD8+ T cells expanded ~70-fold, compared to no expansion after αCD3/28 treatment. After synTac treatment, the HIV-CAR lentivector selectively transduced CMV-specific CD8+ T cells (96% NLV-tetramer+) as compared to αCD3/28-activated HIV-CAR CD8+ T cells (8.8% NLV-tetramer+). Perforin expression by synTac-generated HIV-CAR-T cells was 3.2-fold higher than those generated by αCD3/28. After 2-day coculture, synTac- and αCD3/28-generated CAR-T cells (E:T ratio of 1:1) suppressed HIV infection by 91.5% and 40.8%, respectively. SynTac-generated HIV-CAR-T cells suppressed HIV infection in humanized mice by 95.9% as compared to untreated animals

**Conclusion:** CMV-synTac selectively activates and expands CMV-specific CD8 T cells, enabling their selective transduction with an HIV-CAR lentivector and conversion into HIV-CAR-T cells with more potent suppressive HIV activity than standard αCD3/28-generated HIV-CAR-T cells. CMV-synTac-generated HIV-CAR-T cells potently suppressed HIV infection in humanized mice. These results support a new strategy to generate more potent HIV-CAR-T cells.



## 278 PRECLINICAL STUDIES TOWARD A PHASE I/IIA TRIAL USING ANTI-HIV DuoCAR-T CELL THERAPY

**Kim Anthony-Gonda**[1], Alex Ray[2], Yuge Wang[3], Hang Su[2], Ariele Block[2], Danica Lee[2], Sarah Kleinsorge-Block[4], Jane Reese[4], Marcos de Lima[4], Dimiter S. Dimitrov[5], Rimas Orentas[1], Steven G. Deeks[6], Harris Goldstein[2], Boro Dropulic[1]
*[1]Caring Cross, Gaithersburg, MD, USA, [2]Albert Einstein College of Medicine, Bronx, NY, USA, [3]Lentigen, Gaithersburg, MD, USA, [4]University Hospitals Cleveland Medical Center, Cleveland, OH, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]University of California San Francisco, San Francisco, CA, USA*

**Background:** Anti-HIV chimeric antigen receptor (CAR) T cell therapies are candidates to functionally cure HIV infection in people with HIV (PWH). Paramount to translating such therapeutic candidates successfully into PWH will require anti-HIV CAR-T cells to traffic to lymphoid tissues in the body and eliminate reactivated HIV-infected cells. We hypothesized that clinical-grade anti-HIV duoCAR-T cells could traffic to the site of HIV infection in the spleen of humanized mice with HIV and potently suppress HIV infection.

**Methods:** To test our hypothesis, we developed a GMP-complaint CAR-T cell manufacturing process using the CliniMACS Prodigy device to generate anti-HIV duoCAR-T cells at clinical scale. Clinical-grade anti-HIV duoCAR-T cells (2 x 10^6 total T cells) were intravenously injected into the tail-veins of PBMC-humanized NSG mice with intrasplenic HIV infection (hu-spl-PBMC-NSG). After 17-18 days of HIV infection, humanized mice were evaluated for signs of CAR-related toxicity and HIV infection quantified in the spleens of infected mice treated with and without duoCAR-T cell therapy.

**Results:** IND-enabling studies demonstrated that a single intravenous injection of clinical-grade anti-HIV duoCAR-T cells trafficked from the peripheral blood to the site of HIV infection in the spleen of mice with HIV and eliminated HIV-infected PBMCs. Anti-HIV duoCAR-T cells showed no apparent signs of CAR-related toxicity in humanized mice. Last, and in preparation for our clinical trial, we demonstrated our ability to successfully manufacture high quality anti-HIV duoCAR-T cell products from PWH in the absence of antiretroviral drugs using a GMP-complaint CAR-T cell manufacturing process.

**Conclusion:** This work supports the initiation of our presently open phase I/IIa clinical trial (NCT04648046) to evaluate the safety and efficacy of anti-HIV duoCAR-T cell therapy in PWH.

## 279 CD64 GENE-MODIFIED PRIMARY NK CELLS LOADED WITH ANTI-HIV bNAbs TRIGGER HIGH ADCC

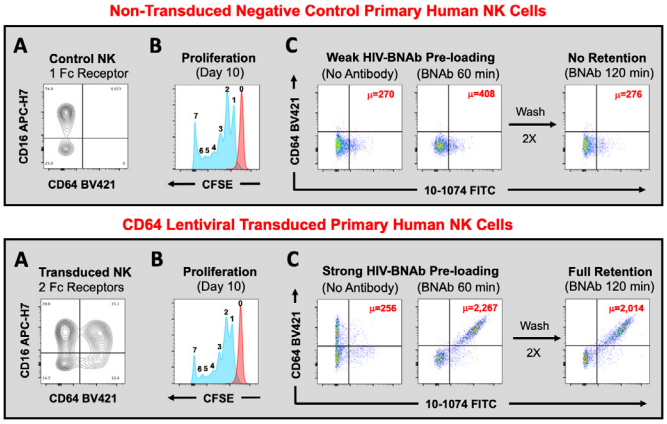
**Costin Tomescu**[1], Hong Kong[2], Meizan Lai[2], James L. Riley[2], Luis J. Montaner[1]
*[1]Wistar Institute, Philadelphia, PA, USA, [2]University of Pennsylvania, Philadelphia, PA, USA*

**Background:** As part of a combined HIV CURE immuno-therapy strategy, we transduced primary human NK cells with the high affinity CD64 Fc receptor and pre-loaded them with HIV-specific bNAbs. We named these chimeric NK cells "NuKES" (NK Enhancement Strategy) for their augmented capacity to mediate ADCC and their potential clinical application as an autologous primary NK cell immuno-therapy against HIV.

**Methods:** We transduced primary NK cells from control donors with a lentivirus expressing human CD64 in the presence or absence of irradiated K562 feeder cells expressing co-stimulatory molecules (CD40, 4-1BB) and/or cytokine pre-stimulation (IL-2, IL-21, IL-15). CD64 expressing NK cells were CFSE labeled and expanded ex vivo or FACS sorted at various times post transduction to high purity. CD64 expressing NK cells were then pre-loaded with HIV-specific bNAbs and tested in a functional ADCC CD107a degranulation assay against HIV-1 infected autologous CD4+ primary T cells.

**Results:** After pre-stimulation with cytokines and/or irradiated K562 Feeder Cells, we could routinely achieve (n=5) greater than 40% CD64 expression in primary human NK cells (Day 14 post-transduction shown in Figure 1A). NK cells maintained strong proliferation potential with greater than 6 cells divisions beyond 10 days post transduction as determined by CFSE dilution (Day 10 post-transduction shown in Figure 1B). Phenotypically, CD64 transduced NK cells were similar to control NK cells and possessed strong expression of CD56, CD16, CD69 with intermediate levels of the NK maturation marker CD57. CD64 transduced NK cells could be successfully pre-loaded with HIV-specific bNAbs and possessed an enhanced capacity (GMFI of 2,014 versus 276) to retain 10-1074 for several hours as compared to control NK cells (Figure 1C). Functionally, CD64 transduced NK cells showed a significant two-fold increase in ADCC-triggered degranulation capacity against autologous HIV-1 infected CD4+ primary T cells compared to control NK cells after pre-loading with HIV-specific bNAbs (27.6% versus 13.2% CD107a).

**Conclusion:** Primary human NK cells can be successfully transduced with CD64 and expanded ex vivo to high purity. Preparation of bNAbs specific NuKES represent a viable autologous NK immuno-therapy approach against HIV-1 with potential adaptation for added disease targets (i.e., COVID, Cancer) moving forward.




**CROI Figure: CD64 Transduced Primary Human NK Cells Displayed Stable Fc Receptor Expression, Maintained Strong Proliferation Capacity, and Possessed Increased Potential To Bind HIV-specific BNAbs.** **(A-C)** Primary human NK were isolated from PBMC, CFSE labeled, activated with IL-2/IL-15 and IL-21 and either mock transduced (top panels) or transduced with a lentivirus encoding CD64 (bottom panels). **(A)** CD64 Fc receptor expression remained stable on transduced NK cells for at least 3 weeks post transduction. **(B)** CD64 transduced NK cells maintained strong proliferation potential (Day 10 post-transduction shown). **(C)** CD64 transduced NK cells displayed increased capacity to bind and retain (after 2 washes) HIV-specific BNAbs over time (Day 21 post-transduction shown).

## 280 TARGETING SIGLEC IMMUNE CHECKPOINTS POTENTIATE NK CLEARANCE OF HIV-INFECTED CELLS

New Investigator Scholar

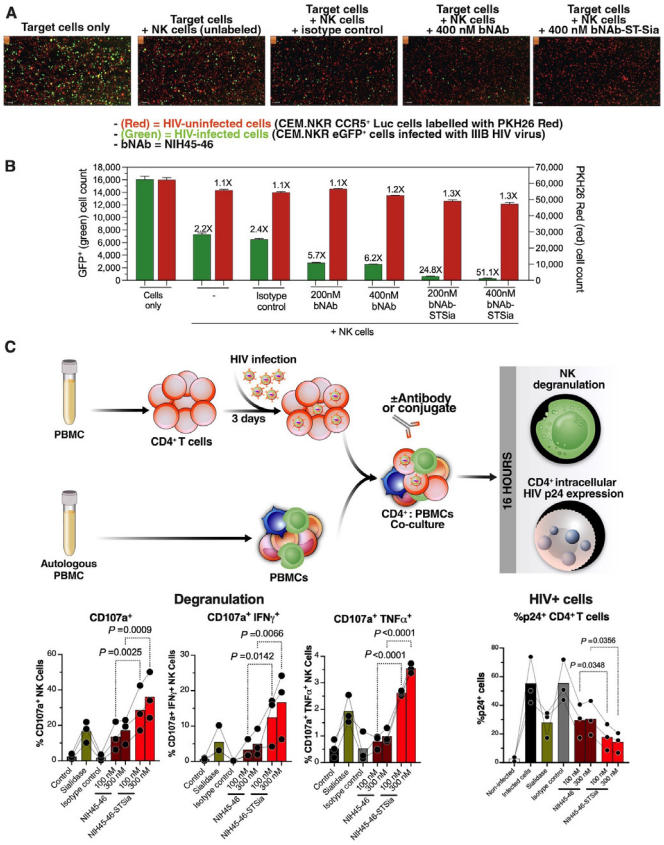
**Opeyemi S. Adeniji**[1], Leticia Kuri-Cervantes[2], Chenfei Yu[3], Ziyang Xu[2], Glen Chew[4], Costin Tomescu[1], Ashley F. George[5], Nadia Roan[5], Lishomwa Ndhlovu[6], Qin Liu[1], Kar Muthumani[1], David Weiner[1], Michael Betts[2], Han Xiao[3], Mohamed Abdel-Mohsen[1]
*[1]Wistar Institute, Philadelphia, PA, USA, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]Rice University, Houston, TX, USA, [4]University of Hawaii, Honolulu, HI, USA, [5]Gladstone Institutes, San Francisco, CA, USA, [6]Weill Cornell Medicine, New York, NY, USA*

**Background:** Siglec-9 is an MHC-independent inhibitory receptor expressed on a subset of the cytolytic CD56dim natural killer (NK) cells. Siglec-9 restrains NK cytotoxicity by binding to sialic acid on the surface of target cells. Despite the importance of Siglec-9 interactions in tumor immune evasion, their role during HIV infection has not been investigated.

**Methods:** We characterized Siglec-9+ CD56dim NK cells from 43 donors: 10 HIV- controls; 11 HIV+ viremic; and 22 HIV+ on suppressive antiretroviral therapy (ART) by flow cytometry. We measured HIV DNA in CD4+ T cells by qPCR. We examined the functional ability of Siglec-9+ and Siglec-9- NK cells to kill HIV+ cells in the presence or absence of Siglec-9 blocking antibody. Finally, we developed a proof-of-concept approach to selectively disrupt Siglec/sialoglycan interactions between NK and HIV+ cells by conjugating Sialidase (an enzyme that removes sialic acid) to several HIV broadly neutralizing antibodies (bNAbs).

**Results:** During HIV infection, Siglec-9+ NK cells exhibit an activated phenotype with higher expression of activating markers (NKp30, CD38, CD16, DNAM-1, perforin) and lower expression of the inhibitory receptor NKG2A ($P<0.05$), compared to Siglec-9- NK cells. Levels of Siglec-9+ CD56dim NK cells inversely correlate with viral load during viremic infection and CD4+ T cell-associated HIV DNA during suppressed infection. In cytotoxicity assays, Siglec-9+ NK cells exhibit higher cytotoxicity towards HIV+ cells compared to Siglec-9- NK cells ($P<0.05$). These data are consistent with the concept that Siglec-9+ NK cells are highly cytotoxic against HIV+ cells. Moreover, blocking Siglec-9 enhanced NK cell ability to lyse HIV+ cells ($P<0.05$), consistent with the known inhibitory function of Siglec-9. Together, these data support a model in which the Siglec-9+ NK subpopulation is cytotoxic against HIV+ cells even whilst being restrained by the inhibitory effects of Siglec-9. To harness the cytotoxic capacity of the Siglec-9+ NK cells, which Siglec-9 dampens, we conjugated Sialidase to bNAbs. These bNAb-sialidase conjugates selectively desialylated HIV+ cells and enhanced NK cells' capacity to kill them using cell line models and autologous primary cell-based killing assays (Fig).

**Conclusion:** We identified a novel glyco-immune checkpoint mechanism that may contribute to the ability of HIV+ cells to evade NK immunosurveillance and developed an approach to break this interaction and enhance the susceptibility of HIV+ cells to NK-mediated clearance.




## 281 IMMUNE RESPONSES FOLLOWING ANTI-PD-1 MONOCLONAL ANTIBODY INFUSION IN PERSONS WITH HIV

**Bernard J. Macatangay**[1], Cynthia Gay[2], Ashley McKhann[3], Ronald J. Bosch[3], Chanelle Wimbish[4], Patrick Mehta[1], Raymond Cha[5], Kendall F. Moseley[6], Cheryl Jennings[7], Danielle Campbell[8], Elizabeth Miller[9], Randall Tressler[10], Daniel Kuritzkes[11], Joseph J. Eron[2], David W. Hardy[12]

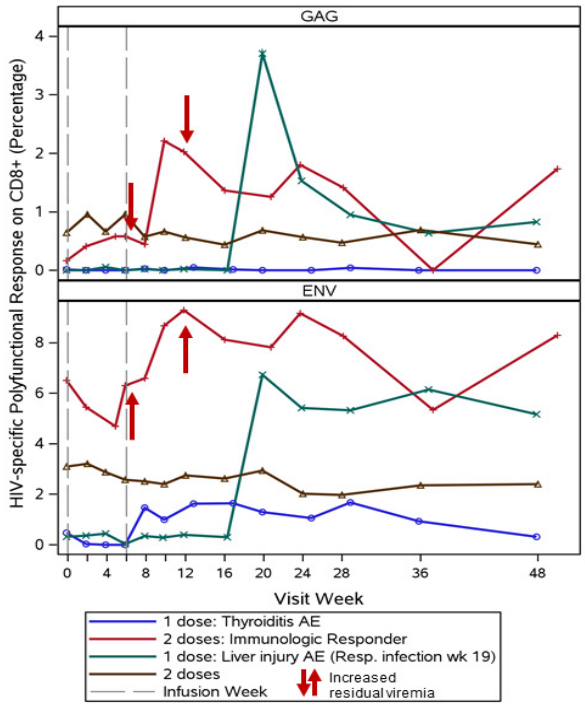
*[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]Harvard TH Chan School of Public Health, Boston, MA, USA, [4]ACTG Network Coordinating Center, Silver Spring, MD, USA, [5]State University of New York at Buffalo, Buffalo, NY, [6]The Johns Hopkins Hospital, Baltimore, MD, USA, [7]Rush University, Chicago, IL, USA, [8]University of California Los Angeles, Los Angeles, CA, USA, [9]Regeneron Pharmaceuticals, Inc, Tarrytown, NY, [10]National Institute of Allergy and Infectious Diseases, Washington, DC, USA, [11]Brigham and Women's Hospital, Boston, MA, USA, [12]The Johns Hopkins University, Baltimore, MD, USA*

**Background:** PD-1 expression on T cells is associated with cellular exhaustion in HIV. We evaluated multiple immunologic parameters following infusion of cemiplimab, an anti-PD1 monoclonal antibody, in ART-suppressed persons with HIV (PWH) in ACTG A5370.

**Methods:** Using flow cytometry, we evaluated changes in CD4+ and CD8+ T cell polyfunctional responses (≥2) to HIV peptide pools by measuring intracellular expression of CD107a, IFNγ, TNFα, and/or IL-2 at baseline and at set timepoints post-infusion of cemiplimab. Concurrently, we determined frequencies of T cells expressing PD1 and other inhibitory receptors (IR): CTLA4, TIM3, TIGIT, LAG3, and PDL1. Residual viremia was measured using a single copy assay.

**Results:** Four participants received 0.3mg/kg cemiplimab infusions; two at week 0 only due to immune related adverse events (irAE) and two at weeks 0 and 6. Enrollment was stopped due to one probable Gr 2 thyroiditis and one possible hepatic irAE. PD-1 receptor occupancy remained >70% 4 to 8 weeks after the last dose. Among four participants who received ≥ 1 dose of cemiplimab, the percentage of gag-specific polyfunctional CD8+ T cells increased 2.2-fold from baseline to post-infusion timepoints (mean of weeks 2 to 12); percentage of gag-specific polyfunctional CD4+ T cells increased 1.8-fold. One participant who received 2 doses had a +6.2-fold and +3.4-fold change in CD8+ and CD4+ polyfunctional T cells to weeks 2-12, respectively (red line in Figure). Increased CD8+ and CD4+ T cell polyfunctional responses persisted through week 28. In this participant, residual viremia increased from 2.5 cps/mL (baseline) to 4.3 (week 6) and 8.1 (week 12). Baseline median frequencies of CD4+ and CD8+ PD-1+ T cells for the 4 participants were 3.4% and 6.7%. The participant with immunologic responses and residual viremia had baseline percentages of PD1+ CD4+ and CD8+ T cells of 7.1% and 7.3%, respectively. Post-infusion, percentages of CD4+ and CD8+ T cells expressing ≥2 IRs in this participant were similar or lower than baseline.

**Conclusion:** We observed a possible immunologic response in 1 of 4 participants who received at least one dose of 0.3 mg/kg cemiplimab. The responding participant had the highest percentage of CD4+ T cells expressing PD1 at baseline and an increase in residual viremia post-infusion which may indicate immunologic and virologic responses following IR-blockade therapy among PWH. The benefits of this therapeutic strategy for HIV remission should be weighed against the potential for irAE.




## 282 CDK INHIBITORS IMPACT HIV-1 SUSCEPTIBILITY BY MODULATING IN VIVO IMMUNOLOGIC RESPONSE

New Investigator Scholar

**Lucía Gutiérrez Chamorro**[1], Eudald Felip[2], Ifeanyi J. Ezeonwumelu[1], Bonaventura Clotet[1], Mireia Margelí[2], Ester Ballana[1]

*[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Catalan Institut of Oncology, Badalona, Spain*

**Background:** Protein kinase inhibitors have been proposed as novel strategies for HIV-1 control, although in vivo evidences from treated patients are limited. Among them, cyclin-dependent kinase inhibitors (CDKi) are orally, well-tolerated drugs currently used for the treatment of metastatic breast cancer (BC), with well-described effects on viral replication and immune cell responses in vitro. Here, using a longitudinal cohort of CDKi-treated BC patients, we determined treatment impact on HIV-1 susceptibility and immune response, in order to define its potential as anti-HIV agents.

**Methods:** Plasma and PBMCs from BC patients treated with CDKi (palbociclib, ribociclib and abemaciclib) were collected before treatment initiation and 3 months afterwards (n=48). Plasma cytokine and inflammation markers were determined by Luminex. Immune cell subsets and T cell immune function in PBMCs were characterized by multicolor flow cytometry. HIV susceptibility was assessed in a subset of patients (n=12) by ex vivo infection with GFP-expressing HIV-1 and in primary cells from healthy controls in vitro treated with CDKi.

**Results:** Immunophenotypic characterization of PBMCs from patients showed no significant changes on major T cell subsets 3-months after CDKi treatment, except for reduced proportion of CD4+ T-central memory cells (p=.028) and decreased expression of the immune exhaustion marker PD1+ (p=.0069), suggesting improved immune cell function in the absence of significant changes in T cell activation. Susceptibility to ex vivo HIV infection was impaired in CDKi-treated compared to untreated samples, an effect that was reversed upon treatment discontinuation, in concordance with in vitro data, where all CDKi inhibited HIV-1 infection in MDMs and CD4+ T-lymphocytes from healthy controls. Interestingly, the percentage of CD4+ T-central memory cells positively correlated with HIV-1 infection (rho=.7436, p=.006), further demonstrating the direct impact of in vivo CDKi treatment on CD4+ T-cell populations and HIV-1 susceptibility. Plasma cytokine expression also showed a modulation of antiviral immune response 3 months after treatment initiation, presenting significantly less EGF (p=.02) and a trend to increased IL-10.
**Conclusion:** In vivo treatment with CDKi turns immunologic responses to a phenotype eventually favouring HIV-1 control by decreasing immune exhaustion and cells representing the main source of virus reservoir; thus, demonstrating the potential of CDKi as putative therapeutic strategy against HIV.

## 283 PROMOTING RESIDENT MEMORY CD8+ T-CELL PHENOTYPES TO ENHANCE HIV RESERVOIR ELIMINATION

**Sebastián G. Kuguel**[1], Nuria Massana[1], Jon Cantero-Pérez[1], Marina Suppi[1], Judith Grau-Expósito[1], Josep Castellví[1], Laura Mañalich-Barrachina[2], Cristina Centeno-Mediavilla[2], Jordi Navarro[1], Adrià Curran[1], Vicenç Falcó[1], Maria José Buzón[1], Meritxell Genescà[1]
*[1]Vall d'Hebron Research Institute, Barcelona, Spain, [2]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain*

**Background:** The major hurdle to HIV-1 eradication is the establishment of viral reservoirs. In tissues, where most of the HIV burden persists, antiviral resident memory CD8+T cells (TRM) may be critical to eliminate cellular reservoirs and transcriptionally-active infected cells. Here we aimed to address the functional capacity of CD8+TRM phenotypes and the control they exert on the viral reservoir.
**Methods:** CD8+TRM cells from cervical tissues were phenotyped by FACS (n=35). In ART-suppressed HIV+ women, we determined total vDNA in blood (n=8) and cervix (n=7) and its correlation with the frequency of cervical CD8+TRM, as well as Gag-specific CD8+TRM in cervical biopsies (n=6). A functional assay was established to assess suppression of reactivated CD4+T cells by cervical CD8+TRM from an ART-suppressed HIV+ woman undergoing hysterectomy. To expand TRM -like phenotypes from circulating CD8+T cells, PBMC obtained from ART-suppressed HIV+ patients were treated with cytokines, degranulation and IFNg secretion were measured in expanded Gag-specific CD8 T cells (n=7) by flow cytometry. Last, a functional assay was established to evaluate the capacity of CD8+T cells from PBMC-expanded cells to eliminate the autologous HIV reservoir after viral reactivation ex vivo (n=6).
**Results:** In cervix, >90% of CD69+CD8+T cells were compatible with belonging to bona fide CD8+TRM, as determined by CCR7, S1PR1, T-bet, Eomes, Hobit, α1 and PD-1 expression. Cervical samples from ART-suppressed patients had higher frequencies of CD8+TRM ($p<0.05$) together with more expression of HLA-DR (p=0.0008). The frequency of cervical CD8+TRM cells were inversely correlated with proviral HIV-1 DNA in cervix (n=7; p=0.03). Gag-specific CD8+TRM were rarely detected in biopsies, which was likely limited by sample size. Still, cervical CD8+TRM cells from the HIV-infected woman with a large sample were more efficient at eliminating HIV-reactivated CD4+T cells than circulating effector CD8+T cells. Circulating Gag-specific CD8+ T cells presented higher expression of CD107a and IFNg after treatment with cytokines for TRM-like induction, together with more capacity to eliminate reactivated HIV-infected cells (p=0.031).
**Conclusion:** Our results highlight an active role of CD8+ TRM phenotypes in limiting tissue viral persistence. Overall, we provide evidences that CD8+TRM-like phenotypes should be potentiated to enhance control of viral persistence and identify a promising immunotherapeutic strategy to help achieve control of reactivated viruses.

Cytokine-expanded CD8+T cells display enhanced elimination of the viral reservoir

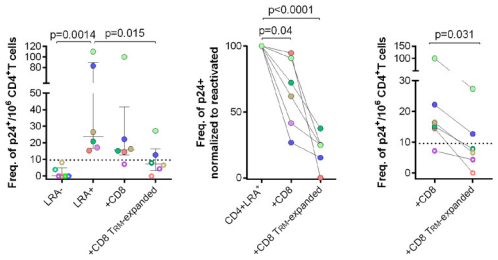



**Fig. Elimination of autologous reactivated CD4+T cells by TRM-like expanded CD8+T cells in ART-suppressed patients.** a, Number of p24 positive cells per million CD3+ CD8-T cells by flow cytometry in the study condition: baseline (not reactivated, LRA-), or after reactivation with Ingenol as a latency reversal agent (LRA+) alone, or in the presence of CD8+T cells 1:1 that were previously cultured for 6 days without or with TRM-inducing cytokine stimulation. Each color represents an individual patient (n=6). Open symbols are below limit of detection (9.6 molecules/106 CD4+T cells), which is indicated with a dotted line. Statistical comparisons were performed using non-parametric Friedman with Dunn's multiple comparison test (two-sided). b, Killing capacity of untreated and cytokine-treated CD8+T cells normalized to detection of p24 in reactivated CD4+T cells as 100%. Statistical comparisons were performed using non-parametric one-way ANOVA followed by Dunnett's multiple-comparisons test (two-sided). c, Paired comparison of the detection of p24 expression per million CD3+ CD8-T cells after addition of untreated and cytokine-treated CD8+T cells (1:1). Statistical comparisons were performed using two-sided nonparametric Wilcoxon matched-pairs signed rank test to compare the two groups.

## 284 INCLUDING Env IN AN HIV THERAPEUTIC VACCINE BLUNTS Gag/Pol-SPECIFIC T-CELL RESPONSES

**Kara W. Chew**[1], Emma Reuschel[2], Mansi Purwar[2], Megan C. Wise[2], Nilu Goonetilleke[3], Elizabeth R. Wonderlich[4], Faraz Zaidi[2], Drew Frase[2], Jean Boyer[5], Laurent Humeau[5], Rafick-Pierre Sékaly[6], David Weiner[2], Dave Glidden[7], Steven G. Deeks[7], Rachel L. Rutishauser[7]
*[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Wistar Institute, Philadelphia, PA, USA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Southern Research, Frederick, MD, USA, [5]Inovio Pharmaceuticals, Inc, Plymouth Meeting, PA, USA, [6]Emory University, Atlanta, GA, USA, [7]University of California San Francisco, San Francisco, CA, USA*

**Background:** T cell-based therapeutic vaccination is a potential approach to achieving durable control of HIV. It is assumed, but has not been thoroughly evaluated, that inclusion of Env antigens in a therapeutic vaccine may blunt immunologic responses to key conserved Gag and Pol targets. We evaluated the impact of including Env on Gag- and Pol-specific T cell responses in an HIV-1 DNA therapeutic vaccine trial.
**Methods:** We conducted a two-site randomized, blinded, placebo-controlled clinical trial ("PENNVAX", NCT03606213) of people with HIV (PWH) on suppressive ART for ≥2 years who initiated ART ≥6 months after infection. Participants were randomized 1:1:1 to receive DNA vaccine encoding multiclade consensus HIV-1 Gag+Pol (G/P)+IL-12, Gag+Pol+Env (G/P/E)+IL-12, or placebo delivered by intramuscular injection/electroporation, stratified on CD4 nadir (<200 or ≥200 cells/$mm_3$) and enrollment site. Vaccine/placebo was administered at Weeks 0, 4, 8, and 12. T cells in peripheral blood mononuclear cells (PBMCs) reactive to vaccine-matched peptide pools or pools spanning highly conserved regions of Gag and Pol were measured pre- and post-vaccination (Week 14) by IFNγ ELISpot. Inducible HIV reservoir measurements were evaluated by differentiation quantitative viral outgrowth assay (dQVOA).
**Results:** Forty-five participants were enrolled, with mean age 51.3 years, 51 (91%) male, 13 (23%) Hispanic/Latinx, and 7 (13%) Black. Vaccination was safe with no unexpected adverse events. Among G/P recipients, median (interquartile range, IQR) fold change (FC) in the magnitude of vaccine-matched Gag- and Pol-specific T cell responses were 2.10 (0.99-3.11; p=0.027) and 2.44 (0.90-3.62; p=0.04), respectively. G/P vaccination also appeared to increase T cell responses to conserved Gag and Pol regions. In contrast, G/P/E vaccination did not significantly increase Gag- or Pol-specific T cell responses. Overall, 62% (8/13) of G/P, 47% (7/15) of G/P/E, and 20% (3/15) of placebo recipients had a ≥2-fold increased magnitude of either vaccine-matched Gag- or Pol-specific T cell responses. Vaccination did not impact inducible HIV levels.
**Conclusion:** We demonstrate that the inclusion of Env sequences in a DNA therapeutic vaccine for HIV hampers enhancement of T cell responses to Gag and Pol in long-term ART-suppressed PWH. While DNA vaccination can boost HIV-specific T cell responses, overall vaccine responses were modest, without impact on the inducible HIV reservoir.

Table. HIV Gag- and Pol-specific T cell responses to HIV therapeutic DNA vaccination (IFNγ ELISpot).

| HIV antigen (vaccine-matched peptide pools) | Arm | Ratio of HIV-specific T cell response magnitude: W14 vs pre-vaccine Median (IQR) | Within-arm p-value, W14 vs pre-vaccine* | Between-arm p-value (vs placebo)** |
|---|---|---|---|---|
| Gag | Gag/Pol/IL-12 (n=13) | 2.10 (0.99-3.11) | 0.03 | <0.01 |
| | Gag/Pol/Env/IL-12 (n=15) | 1.31 (0.94-2.07) | 0.15 | 0.089 |
| | Placebo (n=15) | 0.95 (0.48-1.36) | 0.56 | -- |
| Pol | Gag/Pol/IL-12 (n=13) | 2.44 (0.90-3.62) | 0.04 | 0.12 |
| | Gag/Pol/Env/IL-12 (n=15) | 1.38 (0.97-2.33) | 0.11 | 0.35 |
| | Placebo (n=15) | 1.12 (0.83-1.73) | 0.30 | -- |

*Wilcoxon Signed Rank Test, **Wilcoxon Rank Sum Test; W14 = Week 14

## 285 CONSERVED-REGION MVA VACCINES REDIRECT HIV T-CELL IMMUNODOMINANCE IN PWH ON ART

**Nilu Goonetilleke**[1], Yinyan Xu[1], Shahryar Samir[1], Ann Marie Weideman[1], Sallay Kallon[1], Joanna Warren[1], Maria Abad[1], Alison Crook[2], Lawrence Fox[3], Michael Hudgens[1], David M. Margolis[1], Tomas Hanke[2], JoAnn D. Kuruc[1], Cynthia Gay[1]
*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]University of Oxford, Oxford, UK, [3]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

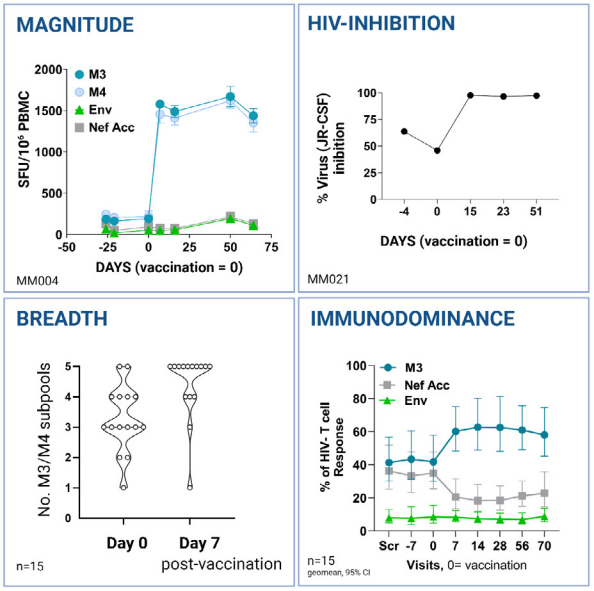
**Background:** Viral mutations rapidly emerge during HIV infection impairing CD8 T cell clearance. These mutations are laid down in the HIV reservoir, compromising host immunity following antiviral treatment interruption. We examined the safety and immunogenicity of MVA-vectored monovalent and bivalent vaccines expressing highly conserved Gag and Pol regions in PWH on ART. In prior studies, we found that T cell escape in these conserved regions is significantly lower than elsewhere in the HIV proteome. We hypothesized that vaccination with conserved-region vaccines will increase HIV-specific T cell immunity and shift T cell immunodominance away from regions harboring higher frequencies of escape.

**Methods:** The M&M Study is a first in human, double-blinded, randomized trial of 24 healthy PWH on ART. Participants received a single intramuscular dose of MVA.tHIVconsv3 (M3), MVA.tHIVconsv4 (M4), combined M3+M4 or saline in a 7:7:7:3 ratio. M3 and M4 are mosaic immunogens, spanning the same 6 HIV regions, differing in 10% of amino acids. Given together, these immunogens may afford greater coverage of HIV diversity. We used ex vivo IFN-γ ELISpot assays to measure changes in T cell magnitude and breadth to M3 and/or M4 HIV immunogens following vaccination. We also examined whether vaccination increased the ability of CD8 T cells to inhibit in vitro HIV replication.

**Results:** We are fully enrolled but are currently blinded. Adverse events likely associated with vaccination were mostly grade 1-2, resolving within 24 hours. Consistent and strong increases in T cell responses to the M3 and M4 HIV immunogens were detected following vaccination, specifically T cell magnitude increased 2- to 18-fold in 13/15 participants tested. M3/M4-specific T cell breadth also consistently increased across participants. Vaccine-associated T cell responses mostly remained elevated (>2-fold increase) for at least 70 days post-vaccination visit. Vaccination was also associated with sustained increases in HIV inhibition in vitro. The percentage of the total HIV-specific T cell response targeting conserved HIV regions increased, on average, from 40 to 60% post-vaccination in participants.

**Conclusion:** Vaccination with MVA-vectored, T cell vaccines expressing conserved mosaic immunogens was safe and well tolerated. Blinded data suggest that M3 and M4 vaccination is strongly immunogenic and successfully shifts T cell dominance (magnitude and breadth) to conserved regions of HIV. Unblinded safety and immunogenicity data will be presented.

**Fig 1. Conserved immunogen, MVA-vectored vaccines (M3, M4) improve HIV T cell immunity in PWH on ART**




## 286 DENDRITIC CELL VACCINATION AGAINST HIV ALTERS NK CELL FREQUENCY AND PHENOTYPE

**Thessa Laeremans**[1], Cynthia Lungu[2], Sabine Den Roover[1], Sigrid D'Haese[1], Rob Gruters[2], Sabine D. Allard[3], Joeri L. Aerts[1]
*[1]Vrije Universiteit Brussel, Brussels, Belgium, [2]Erasmus University Medical Center, Rotterdam, Netherlands, [3]Universitair Ziekenhuis Brussel, Brussel, Belgium*

**Background:** Natural killer (NK) cells play an essential role in the antiviral immune response. Moreover, dendritic cell (DC)-NK crosstalk has been described extensively. However, their role in dendritic cell (DC)-based therapeutic vaccination against HIV remains understudied. Therefore, we aimed to investigate whether DC-based vaccination affects NK cell frequency and phenotype by analysing samples from a previously performed therapeutic vaccination study (Allard et al., Clin. Immunol., 2012).

**Methods:** HIV-1 infected individuals stable on combined antiretroviral therapy (cART), received 4 vaccinations with autologous DCs electroporated with mRNA encoding Tat, Rev and Nef, after which cART was interrupted (ATI). PBMCs were collected at different time points: before vaccination (baselin; N=8), 1 week after second vaccination (vac#2 + 1w; N=9), 4 weeks after ATI (ATI+4w; N=8) and 16 weeks after ATI (ATI+16w; N=8). Phenotyping of NK cells was performed using an extensive flow cytometric panel including inhibitory (KIR2DL1, KIR2DL2/3 and KIR3DL1) and activating receptors (NKG2D and NKp46), immune checkpoint molecules (ICM; PD-1, LAG-3 and Tim3) and receptors involved in homing to the lymph node follicles (CXCR5, CCR7 and CD62L).

**Results:** We observed that the DC-vaccine induced an increase in the number of cytotoxic CD56dimCD16+ NK cells compared to baseline (median of 4.93% and 1.8%, respectively) whereas the number of non-cytotoxic CD56dimCD16- NK cells decreased (median of 0.8% and 8.03%, respectively). After ATI, the number of CD56dimCD16+ NK cells remained stable (0.4%) and the number of CD56dimCD16- NK cells increased again to even higher levels than at baseline (median of 0.24% at baseline, 0.52% at vac#2+1w, 0.64% at ATI+4w and 1.07% at ATI+16w). Additionally, we observed an overall increase in KIR receptors and CD62L expression whereas a decrease in ICM and CCR7 expression was observed after vaccination. After ATI, an increase in NKG2D and CCR7 was observed which declined again after ATI+16w. Expression of KIR receptors remained stable after ATI+4w and ATI+16w. All ICM were increased after 4 weeks and 16 weeks of ATI, which might be indicative for NK cell activation or even exhaustion in a later stage.

**Conclusion:** This work shows that our autologous therapeutic DC-vaccine increases the number of NK cells and affects NK cell phenotype. This highlights the importance of NK cells after DC immunotherapy in HIV infection which should be taken into account for future clinical trials.

## 287 EX VIVO ASSAY PREDICTS HIV-1 SUPPRESSION BY bNAbs INFUSED IN A PHASE I CLINICAL TRIAL

**Sabrina Helmold Hait**[1], Sarah E. Lovelace[2], Emily E. Coates[1], Grace Chen[1], Martin R. Gaudinski[1], Ro Shauna Rothwell[1], Eileen Donaghy[3], Jhoanna Roa[4], Carl J. Fichtenbaum[5], Jorge Santana[6], Rachel Presti[7], Pablo Tebas[3], Julie E. Ledgerwood[1], Amarendra Pegu[1], John R. Mascola[8]

*[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [2]National Institutes of Health, Bethesda, MD, USA, [3]University of Pennsylvania, Philadelphia, PA, USA, [4]DLH Corporation, Philadelphia, PA, USA, [5]University of Cincinnati, Cincinnati, OH, USA, [6]University of Puerto Rico, San Juan, PR, USA, [7]Washington University in St Louis, St Louis, MO, USA, [8]National Institute of Allergy and Infectious Diseases, Hamilton, MT, USA*

**Background:** Broadly neutralizing antibodies (bNAbs) target conserved regions of the HIV-1 envelope and show potential as complementary immunotherapy to combination anti-retroviral therapies (cART) for HIV-1 treatment. However, infusion of a single bNAb in viremic individuals results in selection for escape variants that are likely part of the individuals viral quasispecies. To better predict the potential for a bNAb to induce an in vivo virologic response, we developed an ex vivo assay that assesses bNAb virologic in people with HIV.

**Methods:** CD4+ T cells were isolated from blood of viremic subjects with HIV enrolled in VRC607/ACGT5378, a phase I study investigating antiviral efficacy of VRC01LS or VRC07-523LS, both targeting the CD4 binding site on the HIV-1 envelope glycoprotein. CD4+ cells obtained prior to bNAb infusion were activated and co-cultured with CD4+ T cells from individuals without HIV to stimulate viral replication and subjected to treatment with various bNAbs at a concentration of 75 mcg/ml, including those administered in the clinical trial. To evaluate viral replication, longitudinal HIV p24 ELISA was performed using culture supernatants.

**Results:** In VRC607/ACGT5378, 7 viremic subjects were infused with VRC01LS and 9 with VRC07-523LS. Two subjects infused with VRC01LS and 8 infused with VRC07-523LS demonstrated a greater than 1 $log_{10}$ decline of viremia following bNAb administration. The results of ex vivo assays performed so far are in accordance with the virological outcome observed in these patients following bNAb treatment. Assays using samples from 3 subjects exhibiting a greater than 1 $log_{10}$ decline of viremia to VRC01LS or VRC07-523LS (in vivo response) evidenced greater than 10-fold reduction in viral replication by the corresponding bNAb relative to the assay control (ex vivo response). Moreover, assays using CD4+ T cells from 4 subjects that did not show in vivo viral suppression after bNAb infusion also failed to control replication in the ex-vivo assay when evaluated with the respective bNAb, indicating the ex vivo assay successfully mimicked clinical trial outcomes.

**Conclusion:** These data compare the in vivo and ex-vivo effect of HIV-1 bNAbs and suggest that the ex vivo assay has the potential to reliably predict the antiviral effect of bNAbs in clinical trials. Because it is possible to test multiple bNAbs in the assay, it could be an effective tool for preclinical testing and selection of the most efficacious bNAb or bNAb combinations to advance to clinical trials.

## 288 ChAdOx1 nCoV-19 VACCINATION IN PWH: IMMUNE RESPONSES TO SARS-CoV-2, VOCs, AND HCoVs

New Investigator Scholar

**Ane T. Ogbe**[1], Matthew Pace[1], Mustapha Bittaye[1], Stephanie Longet[1], Tom Tipton[1], Wanwisa Dejnirattisai[1], Katie J. Ewer[1], Gavin R. Screaton[1], Sarah C. Gilbert[1], Miles Carroll[1], Andrew J. Pollard[1], Sarah Fidler[2], Julie Fox[3], Teresa Lambe[1], John Frater[1]

*[1]University of Oxford, Oxford, UK, [2]Imperial College London, London, UK, [3]Guy's and St Thomas' NHS Foundation Trust, London, UK*

**Background:** People living with HIV (PWH) may represent a high-risk group for adverse clinical outcomes from SARS-CoV-2. The duration of protection from SARS-CoV-2 and emerging variants of concern (VOC) infection in PWH following vaccination is unclear. Furthermore, the role of preexisting SARS-CoV-2 immune responses, likely acquired from prior exposure to circulating human coronaviruses (HCoVs), on vaccine-mediated immunity remains to be determined. Understanding the kinetics of immune responses to SARS-CoV-2 and VOCs, and the impact of preexisting SARS-CoV-2 immunity on vaccine-mediated immune responses will be critical in informing COVID-19 vaccination policies in PWH.

**Methods:** In this sub-study of the Phase II/III COV002 trial (open-label, non-randomised clinical trial ID: NCT04400838), 54 HIV+ male participants on antiretroviral therapy (undetectable viral loads, CD4+ T cells >350 cells/ul) and 50 HIV- sex and age-matched controls received two doses of ChAdOx1 nCoV-19 (AZD1222) 4-6 weeks apart and were followed for 6 months. Immune responses to vaccination were determined by ELISA (standard and MSD assay), neutralisation, ACE-2 inhibition, IFNγ ELISpot, activation-induced marker (AIM) assay and T cell proliferation assays.

**Results:** 6 months after vaccination, antibody IgG levels to SARS-CoV-2 S and RBD proteins, ACE-2 inhibition and T cell responses to S protein were significantly higher than baseline (Table 1). Both humoral and cell-mediated immunity waned over time, but with no significant difference compared with HIV- individuals vaccinated with the same regimen. T and B cell-mediated immune responses to VOCs α, β, γ, and δ were detectable, although at lower magnitudes than wild type. Prior exposure to circulating β coronavirus HKU1 and OC43 was associated with measurable proliferative SARS-CoV-2 T cell response at baseline and a higher magnitude of post-vaccine T cell responses.

**Conclusion:** Our data demonstrate no significant difference in ChAdOx1 nCoV-19 vaccine-mediated immune responses by HIV status. For all groups, we show waning but detectable immune responses against SARS-CoV-2 and VOCs 6 months after vaccination supporting the on-going policy to vaccinate against SARS-CoV-2 and reinforces the argument for long-term monitoring of responses.

| | Antibody (n = 42) | | | IFNγ ELISpot (n = 37) | T cell proliferation assay (n = 47) | | | |
|---|---|---|---|---|---|---|---|---|
| | S | RBD | ACE-2 inhibition assay | SFU/10^6 | CD4+ S1 (%) | CD4+ S2 (%) | CD8+ S1 (%) | CD8+ S2 (%) |
| Day 0 IQR | 21.1 - 118 | 46.4 - 217.4 | 0.2 - 0.46 | 48 - 121 | 0.13 - 2.5 | 0.23 - 2.6 | 0.03 - 0.9 | 0.02 - 1.3 |
| Day 182 IQR | 1336 - 6670 | 719 - 3885 | 0.8 - 1.5 | 133 - 572 | 1.2 - 5.4 | 0.6 - 4.3 | 0.37 - 2.8 | 0.12 - 2.7 |
| P value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.001 | <0.01 | <0.0001 | <0.001 |

**Table 1:** IQR and P values for humoral and cell-mediated immune responses following ChAdOx1 nCoV-19 vaccination in PWH

## 289 HIGH SEROCONVERSION RATE AND DELTA NEUTRALIZATION IN PLWHIV VACCINATED WITH BNT162b2

**Valérie Pourcher**[1], Lisa Belin[1], Cathia Soulie[1], Michelle Rosenzwajg[1], Stéphane Marot[1], Karine Lacombe[1], Nadia Valin[1], Gilles Pialoux[1], Ruxandra Calin[1], Roland Tubiana[1], Marc Antoine Valantin[1], David Klatzmann[1], Vincent Calvez[1], Noémie Simon-Tillaux[1], Anne Genevieve Marcelin[1]

*[1]Assistance Publique–Hôpitaux de Paris, Paris, France*

**Background:** The emergence of SARS-CoV-2 variants is a major concern. As the Delta variant became dominant worldwide, obtaining specific data on the humoral and cellular responses after BNT162b2 vaccination against this variant of concern in PLWHIV is crucial.

**Methods:** Multicenter cohort study of PLWHIV, with a CD4 cell count <500/$mm_3$ and a viral load <50 copies/ml on stable antiretroviral therapy for at least 3 months, to explore humoral and cellular responses to BNT162b2 vaccination. IgG antibodies (Ab) to the Receptor Binding Domain (RBD) of the spike protein and their neutralization capacity, assessed by an ELISA (Genscript) and a virus neutralization test (VNT), against historical strain, Beta and Delta variants were performed before vaccination (day 0) and one month after a complete vaccination schedule (M1).

**Results:** 97 patients were enrolled in the study (table 1. baseline characteristics). Among them, 85 patients received 2 shots (11 previous COVID-19 and 1 premature exit). The median time between the 2 shots was 28 [IQR 28-29] days. 90 patients could be evaluated at M1. The seroconversion rate in anti-RBD IgG was 97% CI95%[90% ; 100% ] at M1. Median (IQR) anti-RBD Ab titer was 0.97 (0.97-5.3) BAU/ml at D0 and 1219 (602-1929) at M1. Neutralizing Ab capacity improved between D0 (15% CI95%[8%;23%]) and M1 (94% CI95%[87% ;98%]) with the Genscript assay. Neutralizing Ab with the VNT were present at M1 for historical strain, Beta and Delta variants in 82%, 77% and 84% patients respectively. Planned subgroups analysis at M1 showed that seroconversion rate and median anti-RBD Ab titer were 91% and 852 BAU/ml in patients with CD4<250/$mm_3$ (n=13) and 98% and 1270 BAU/ml in patients with CD4>250/$mm_3$ (n=64) (difference of change between D0 and M1 between subgroups p=0.8224). 73% of patients with CD4<250/$mm_3$ had neutralizing Ab and 97% of those with CD4>250/$mm_3$ (p=0.0130). The neutralization capacity of beta variant was 50% in CD4<250/$mm_3$ and 81% in CD4>250/$mm_3$ (p=0.0292). No change in CD4+ or CD8+ T cells count was observed while a decrease of CD19+ B cells count was observed (208 ±124/$mm_3$ at D0 vs 188 ±112/$mm_3$ at M1, p<0.01). Tolerance was very good and no COVID-19 was reported until M1.

**Conclusion:** These results show a high seroconversion rate with a Delta neutralization in PLWHIV patients after a complete BNT162b2 vaccination schedule. However, patients with CD4<250/mm$_3$ had a decrease neutralizing Ab capacity mainly against Beta than Delta variant.

**Table 1. Baseline patients characteristics (n = 97)**

| | Median or number | IQR or % |
|---|---|---|
| Age, years | 48 | 39-56 |
| Sex, male | 85 | 87.6% |
| IMC | 24 | 21.9-27.1 |
| Other chronic diseases | 39 | 40.2% |
| Allergia | 5 | 5.1% |
| Hemoglobin | 14.8 | 13.7-15.7 |
| Lymphocytes | 1591 | 1350-1870 |
| ALAT | 25 | 19-36 |
| ASAT | 24 | 19-30 |
| Duration of HIV infection, years | 11,1 | 7.6-22.2 |
| Past history of opportunistic infections | 47 | 48.4% |
| Past history of virological failure | 31 | 31.9% |
| ARV therapy duration, years | 10.3 | 6.5-17.4 |
| Duration of viral load <50 copies/ml, months | 78 | 28-123 |
| Tritherapy | 69 | 71% |
| Bitherapy | 22 | 22.7% |
| CD4 cell count/mm$^3$ | 401 | 303-471 |
| Ratio CD4/CD8 | 0.7 | 0.4-0.9 |

## 290 HOW HIV MODULATES THE SAFETY AND IMMUNOGENICITY OF THE BNT162b2 COVID-19 VACCINE

**Ludovica Ferrari**[1], Lorenzo Piermatteo[1], Federica Caldara[2], Eleonora Andreassi[2], Ada Bertoli[1], Harrison Austin[3], Diletta Meloni[1], Elisabetta Teti[2], Mirko Compagno[1], Marco Iannetta[1], Francesca Ceccherini-Silberstein[1], Loredana Sarmati[2], Massimo Andreoni[1], Anna Maria Geretti[1]

*[1]University of Rome Tor Vergata, Rome, Italy, [2]Hospital of Rome Tor Vergata, Rome, Italy, [3]University of Liverpool, Liverpool, UK*

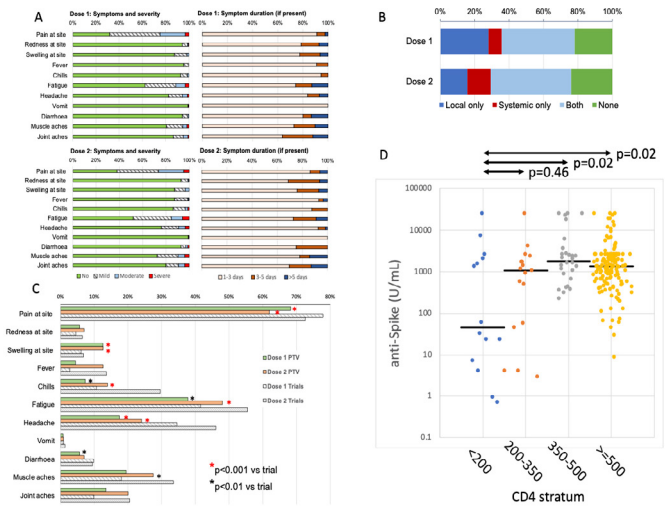
**Background:** The pivotal BNT162b2 trials included only ~60 vaccine recipients, all with well controlled HIV, and there is a need to gather more information on vaccine safety and immunogenicity in diverse populations. This prospective study evaluated solicited and unsolicited adverse events (AEs) and anti-S and anti-NC serological profiles in a diverse cohort of people with HIV undergoing BNT162b2 vaccination (2 doses 3 weeks apart).

**Methods:** Participants completed structured questionnaires modelled on the BNT162b2 trials (FDA submission, Nov 2020) to report solicited and unsolicited AEs in the 7 days after each vaccine dose, indicating severity and duration. Serum samples collected prior to dose-1 (T0) and 3-6 weeks after dose-2 (T1) underwent qualitative anti-NC and quantitative anti-S testing by Elecsys®. Factors associated with T1 anti-S titres were explored in linear regression models including all available parameters.

**Results:** Overall, 259 adults received dose-1 (26% female, 77% white, 44% MSM, 44% history of advanced disease, 31% ≥1 comorbidity, 10% HIV RNA >50 cps/ml [median 122 cps], 7% prior COVID-19 diagnosis, 15% anti-NC positive; median age 48 years, ART duration 7 years, nadir/current CD4 count 225/708 cells/mm$_3$, CD4:CD8 ratio 0.8); 257 received dose-2. Local AEs were more common after dose-1 than dose-2 (70% vs. 62%, p=0.015), whereas systemic AEs increased with dose-2 (50% vs 60%; p=0.006) (Fig 1a-c); 22% experienced moderate-severe systemic AEs after dose-2. Unsolicited AEs (mainly nausea and light-headedness) were reported by 7% after dose-1 and 9% after dose-2. Among 206 participants with T1 samples, 205 (99%) had measurable anti-S (>0.8 U/ml). Anti-S levels were significantly lower at CD4 counts <200 cells/mm$_3$ (Fig 1d). In adjusted regression analyses, factors associated with anti-S titres comprised anti-NC positivity (fold-change 7.39; 95% CI 3.92-13.91; p<0.01), HIV viraemia (FC 0.24; 0.11-0.50; p<0.01), reporting moderate-severe systemic AEs after dose-2 (FC 1.77; 1.03-3.04; p=0.04) and either the CD4 count (FC 1.01; 1.00-1.01; p=0.04) or CD4:CD8 ratio (FC 1.05; 1.00-1.10; p=0.05).

**Conclusion:** In this cohort with HIV, AE patterns after vaccination were similar to those seen in the pivotal BNT162b2 trials and most AEs were mild and short-lived. Whilst prior exposure to SARS-CoV-2 predicted higher anti-S responses, CD4 counts <200 cells/mm$_3$ and low-level viraemia predicted reduced anti-S responses, thus identifying a subset potentially vulnerable to reduced vaccine efficacy.

**Figure 1.** Solicited adverse events after each BNT162b2 vaccine dose (A-C) with severity and duration (A) and in relation to the total population of the pivotal BNT162b2 trials (C), and anti-S titres 3-6 weeks after the second vaccine dose among people with HIV (D)




## 291 DURABILITY OF SARS-CoV-2 mRNA VACCINE IMMUNE RESPONSE IN PLWH WITH ADVANCED DISEASE

**Stefania Cicalini**[1], Alessandra Vergori[1], Alessandro Cozzi-Lepri[2], Silvia Meschi[1], Veronica Bordoni[1], Simone Lanini[1], Daniele Lapa[1], Davide Mariotti[1], Lidya De Pascale[1], Veronica D'aquila[1], Concetta Castilletti[1], Chiara Agrati[1], Enrico Girardi[1], Francesco Vaia[1], Andrea Antinori[1]

*[1]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [2]Centre for Clinical Research, Epidemiology, Modelling and Evaluation, London, UK*

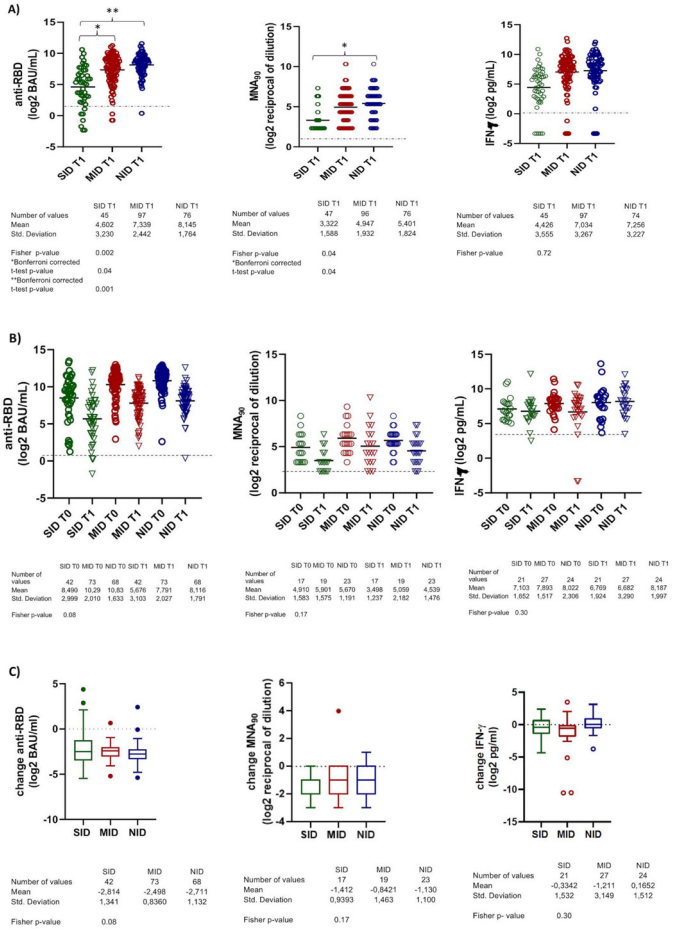
**Background:** Waning of vaccine protection against SARS-CoV-2 infection is currently a concern and durability of specific immunity after vaccination in PLWH is still unknown. The aim of this analysis was to evaluate persistence of immune response to mRNA vaccines in PLWH with advanced disease.

**Methods:** PLWH with a CD4 count ≤200/mm3 and/or previous AIDS, enrolled in a SARS-CoV-2 vaccination program at INMI hospital in Rome, Italy, were evaluated >90 days after 2nd dose of BNT162b2 or mRNA-1273 (time T1). Anti-RBD by CLIA, neutralizing antibody (nAb) titers by microneutralization assay (MNA90) and IFNγ production were assessed and response defined as having anti-RBD >7.1 BAU/mL, nAbs ≥1:10, IFNγ >12 pg/mL. Participants were stratified by CD4 count (severe immunodeficiency, SID, ≤200/mm3; minor immunodeficiency, MID, 201-500/mm3; no immunodeficiency, NID, >500/mm3). Waning of immune response was evaluated in a subgroup of responders for whom two values post 2nd dose were available. Paired t-test was used to test the overall decline. ANOVA and logistic regression analysis controlling for age, viral load, CD4 nadir and cancer were used for comparisons by CD4 groups.

**Results:** 221 pts were included (SID=47; MID=98; NID=76); 81% male; median age 55 yrs (IQR 49-60); median time from HIV diagnosis 7 yrs (3-15); 74% previous AIDS diagnosis; median CD4 nadir 44/mm3 (16-122). All pts receiving ART, 87% with HIV-RNA<50 cp/mL. After a median of 145 (133-157) days after 2nd dose, a detectable anti-RBD response was still present in 83% of SID, 96% of MID and 98% of NID (P=0.0009); nAbs in 38% of SID, 78% of MID and 88% of NID (P<0.0001); IFNγ in 67% of SID, 90% of MID and 92% of NID (P=0.0002). Magnitude of residual immune response at T1 was significantly lower in SID (Figure 1a). By logistic regression, risk of nAbs undetectability was higher in SID (aOR 5.03; 95% CI 1.22-20.81) and in MID (aOR 3.77; 11.4-12.48) vs NID, while no evidence for a difference was found for anti-RBD and IFNγ. A significant decline of immune response was observed for all immune parameters [mean log2 (SD): -2.66 (1.08), p<0.001, for anti-RBD; -1.23 (1.26), p<0.001, for nAbs; and -0.51 (2.3), p=0.05, for IFNγ], regardless of CD4 groups (Figure 1b/c).

**Conclusion:** A high proportion of PLWH with advanced disease showed a lack of immune response after a median of 5 months from SARS-CoV-2 mRNA vaccination, suggesting an urgent need for a booster dose. A current CD4 ≤200/mm3 was associated with higher risk of vanishing of neutralizing activity.

**Figure 1.**
A) Concentrations of anti-RBD ($log_2$ BAU/mL), neutralizing antibody (nAb) titers (expressed as $MNA_{90}$ reciprocal of dilution $log_2$) and IFNγ ($log_2$ pg/mL) in blood samples collected at >90 days (T1) after receipt of the 2nd dose of a mRNA vaccine in 221 PLWH [median time 145 (IQR 133-157) days after 2nd dose], according to CD4 cell count.
B) Waning of anti-RBD, ($log_2$ BAU/mL), neutralizing antibody (nAb) titers (expressed as $MNA_{90}$ reciprocal of dilution $log_2$) and IFNγ ($log_2$ pg/mL) from T0 (one month after 2nd dose of vaccine) to T1 (>90 days after 2nd dose of vaccine), in PLWH eligible for longitudinal observation, according to CD4 cell count.
C) Magnitude of changes of anti-RBD ($log_2$ BAU/mL), neutralizing antibody (nAb) titers (expressed as $MNA_{90}$ reciprocal of dilution $log_2$) and IFNγ ($log_2$ pg/mL) from T0 (one month after 2nd dose of vaccine ) to T1 (>90 days after 2nd dose of vaccine), between CD4 groups.



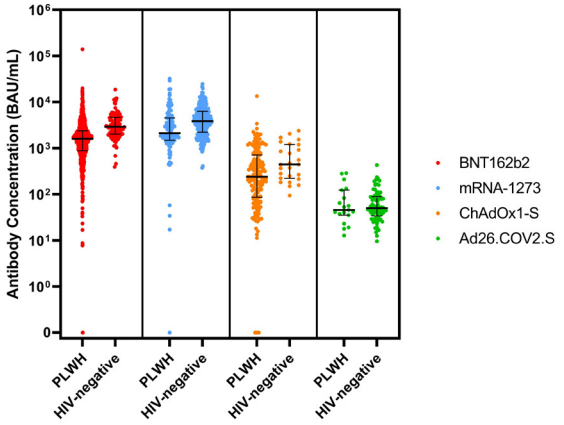

Legend: RBD=receptor binding domain; MNA=microneutralization assay; IFNγ=interferon gamma; SID=severe immunodeficiency (CD4 count ≤200/mm³); MID=minor immunodeficiency (CD4 count 201-500/mm³); NID=no immunodeficiency (CD4 count>500/mm³); T0=one month after 2nd dose of vaccine; T1= >90 days after 2nd dose of vaccine.

## 292 SARS-CoV-2 VACCINE IMMUNOGENICITY IN PLWH IN THE NETHERLANDS

Late Breaking

**Kathryn S. Hensley**[1], Marlou Jongkees[1], Corine H. Geurts van Kessel[1], Virgil A. Dalm[1], Jan G. den Hollander[2], Wouter F W Bierman[3], Eliane M. Leyten[4], Emile F. Schippers[5], Heidi S. Ammerlaan[6], Marc Van der Valk[7], Bart J. Rijnders[1], Kees Brinkman[8], Anna Roukens[9], Casper Rokx[1]
*[1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Maasstad Hospital, Rotterdam, Netherlands, [3]University Medical Center Groningen, Groningen, Netherlands, [4]Haaglanden Medical Centre, The Hague, Netherlands, [5]Haga Teaching Hospital, The Hague, Netherlands, [6]Catharina Hospital, Eindhoven, Netherlands, [7]DC Klinieken, Amsterdam, Netherlands, [8]OLVG, Amsterdam, Netherlands, [9]Leiden University Medical Center, Leiden, Netherlands*

**Background:** Vaccines can be less immunogenic in people living with HIV (PLWH). So far, the immune response after SARS-CoV-2 vaccination of PLWH is not well-established.
**Methods:** A prospective cohort study in 22 HIV treatment centres in the Netherlands examined the immunogenicity of SARS-CoV-2 vaccines in PLWH. Included were adult PLWH without prior COVID-19 infection, invited by the national vaccination programme to receive the BNT162b2, mRNA-1273, ChAdOx1-S or Ad26.COV2.S vaccine. Data from HIV-negative healthy controls were acquired from 2 concurrent prospective vaccination trials. The primary endpoint was the anti-SARS-CoV-2 IgG response (Liaison Trimeric Spike IgG in BAU/ml) measured 4-6 weeks after vaccination with one of the 2 mRNA vaccines in PLWH versus controls. Secondary endpoints included antibody response according to sex, CD4+ T-cell count, and vaccine reactogenicity.
**Results:** Between February 14th and September 7th 2021, 1269 PLWH were enrolled and complete results were available for 1148 PLWH as well as for 440 healthy controls. 879 of the PLWH were vaccinated with BNT162b2 while 100, 150 and 19 had received mRNA-1273, ChAdOx1-S and 19 Ad26.COV2.S respectively. Their median age was 53 years [IQR 44-60], 85.5% was male, the median CD4+ T-cell count was 710/µL [IQR 520-913]. 99% was on cART with HIV-RNA <50 copies/ml in 97.7%. The control group consisted of 440 healthy people; 247 vaccinated with mRNA-1273, 94 with BNT162b2, 26 with ChAdOx1-S and 73 with Ad26.COV2.S. Their median age was 43 [IQR 33-53] and 28.6% was male. PLWH had a significantly lower anti-SARS-CoV-2 RBD IgG response compared to controls (mean value of 2171 BAU/mL (95% CI 1888-2453) versus 3586 BAU/ml (95% CI 3250-3922, p<0.001)). In the multivariable analysis, being HIV positive, age >65 years, being male and having received a non-mRNA vaccination were all independently associated with a lower antibody concentration (p<0.01 for all). In the PLWH vaccinated with BNT162b2 or mRNA-1273, mean antibody levels were significantly lower in those with a CD4+ T-cell counts <250/µL (1617 BAU/mL, 95% CI 828-2407) compared to CD4 ≥250/µL (2486 BAU/ml 95% CI 2149-2824, p=0.002). Reactogenicity occurred in 55 and 50% after the first and second vaccination respectively and were generally mild without vaccine-related SAE.
**Conclusion:** After vaccination with BNT162b2 or mRNA-1273, Anti-Spike IgG levels were lower in PLWH compared to healthy controls. In PLWH, a CD4+ T cell count <250/µL was associated with lower antibody concentration.




Antibody response in binding antibodies per millilitre (BAU/mL) with BNT162b2, mRNA-1273, ChAdOx1-S nCoV-19 and Ad26.COV2.S vaccines in people living with HIV and HIV-negative control group. The thick horizontal bar shows the median, with error bars showing the interquartile range.

## 293 IMMUNOGENICITY TO COVID-19 mRNA VACCINE BOOSTER SHOT IN PLWH BY CURRENT CD4+ COUNT

**Alessandra Vergori**[1], Stefania Cicalini[1], Alessandro Cozzi-Lepri[2], Giulia Matusali[1], Veronica Bordoni[1], Simone Lanini[1], Francesca Colavita[1], Eleonora Cimini[1], Roberta Iannazzo[1], Lidya De Pascale[1], Concetta Castilletti[1], Chiara Agrati[1], Enrico Girardi[1], Francesco Vaia[1], Andrea Antinori[1]
*[1]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [2]University College London, London, UK*

**Background:** In Italy in September 2021, administration of a booster shot (BS) of COVID-19 vaccine was approved for PLWH with advanced disease (current CD4 count<200 cell/mm3 and/or previous AIDS). The aim of this analysis was to investigate the degree of immunogenicity after BS by current CD4 count.
**Methods:** In PLWH attending INMI Spallanzani Hospital in Rome, Italy and receiving a BS of BNT162b2 or mRNA-1273 >28 days after a complete mRNA vaccination cycle, immunogenicity was assessed at time of BS (T0) and at day 15 (T1) by anti-RBD CLIA, microneutralization assay [MNA90] and IFNγ production. Participants were stratified by CD4 count at T0 (severe immunodeficiency, SID: <200/mm3; minor immunodeficiency, MID: 200-500/mm3; no immunodeficiency, NID: >500/mm3). Immune response was defined: anti-RBD >7.1 BAU/mL, MNA90 titres >1:10 and IFNγ >12 pg/mL. A paired t-test was used to test overall changes (log2 scale) over T0-T1. ANOVA and truncated regression models were used to compare change in titers from T0 to T1, association between current CD4 count and the lack of immune response was determined

by fitting a multivariable logistic regression adjusted for age, time from HIV diagnosis, CD4 nadir, cancer and HIV-RNA a T0.

**Results:** We included 216 PLWH on ART (n=76 SID, n=96 MID, n=44 NID): median age 54 yrs (IQR 47-59), median CD4 nadir 45 cell/mm3 (20-122), 93% HIV-RNA <50 c/mL, 7yrs (3-12) since HIV diagnosis and 5yrs (2-8) since AIDS if diagnosed. Participants received BS after a median of 142 (132-156) days from second dose. Response rate was 95.5% in SID, 100% in MID, 100% in NID for anti-RBD (p=0.02); 86.3%, 97.9% and 98.7% for nAbs (p=0.002), and 70%, 95.6% and 97.2% for IFNγ (p<0.0001). Overall we observed a significant increase of BS immunogenicity [anti RBD: mean Log2 4.5 (SD 1.9),p<0.0001; nAbs: 3.7 (2.2),p<0.0001; IFNγ: 0.77 (2.9),p=0.0003]. However, there was no evidence for a difference in mean change of humoral immunogenicity, anti-RBD, nAbs and IFNγ changes by CD4 count groups (Figure 1 A-C). A current CD4 count <200 cell/mm3 was not associated with the risk of failing to elicit neutralizing and cell-mediated response by logistic regression (Figure1D).

**Conclusion:** A mRNA BS strongly boosted humoral response in PLWH with advanced disease, regardless of CD4 count at the time of booster. Although clinical implications of the observed immunological response remain uncertain, our data support the usefulness of BS in PLWH with immune dysregulation.

**Figure 1. A)Results of change of RBD-binding IgG response ($log_2$ BAU/mL), B)$Log_2$ MNA90 and C) IFNγ ($log_2$ pg/mL) in PLWHs from T0 to time of boosted dose (T1) and according to current CD4 T cell count**

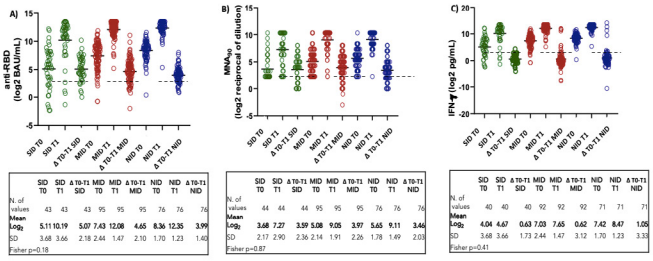
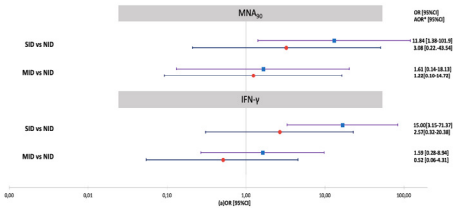



**Figure 1. D) Unadjusted and adjusted OR of failing to achieve detectable levels of $MNA_{90}$ and IFN-γ from fitting a logistic regression controlled for age, time from HIV diagnosis, CD4 nadir, cancer and HIV-RNA at T0**




## 294 ALTERED FEATURES OF B AND T CELL RESPONSES TO BNT162 VACCINE IN HEMODIALYSIS PATIENTS

New Investigator Scholar

**Alexandre Nicolas**[1], Gérémy Sannier[1], Lorie Marchitto[1], Manon Nayrac[1], Nathalie Brassard[1], Shilei Ding[1], Alexandra Tauzin[1], Mathieu Dubé[1], Cécile Tremblay[1], Valérie Martel-Laferrière[1], Rémi Goupil[2], William Beaubien-Souligny[2], Andrés Finzi[1], Rita Suri[3], Daniel E. Kaufmann[1]

*[1]Centre de Recherche du CHUM, Montreal, Canada, [2]Université de Montréal, Montreal, Canada, [3]McGill University, Montreal, Canada*

**Background:** People receiving hemodialysis (HD) are highly vulnerable to SARS-CoV-2 infection and develop lower antibody responses to SARS-CoV-2 mRNA vaccines. However, the underlying immune defects are poorly understood. We compared immune responses of 27 HD patients with 22 health care workers (HCW) before and up to 4 months after 2 doses of BNT162 SARS-CoV-2 vaccination. All participants were confirmed to be SARS-CoV-2 naïve.

**Methods:** We profiled B cells, CD4 T cells, CD8 T cells and humoral responses and examined associations between these arms of immunity. We used high-parameter flow cytometry to study: i) receptor binding domain (RBD)-specific B cells; ii) the phenotype of Spike (S)-specific CD4 and CD8 T cells identified by an activation-induced marker (AIM) assay; iii) effector functions of S-specific CD4 and CD8 T cells by intracellular staining (ICS). We measured humoral responses by ELISA RBD.

**Results:** In each cohort, two vaccine doses enhanced RBD-specific B cell responses, with a significantly greater increase after the second dose (V2 than after the first dose (V1). Their magnitude was significantly lower in HD than in HCW at V1 (p=0.002) and V2 (p=0.002), which was consistent with the detection of lower anti-RBD IgG antibody levels at the same time points (V1: p<0.001; V2: p<0.001). The subsequent rates of B cell decline were similar in HD and HCW. As CD4 help is critical for B cell and CD8 T cell immunity, we compared Spike (S)-specific T cells responses between cohorts. While we observed no significant quantitative difference in the magnitude of vaccine-specific CD4 T cells between HD and HCW at V2, phenotypic and functional Thelper profiles differed significantly. The frequency of vaccine-specific CXCR3+ Th1 CD4 T cells was significantly increased in HD compared to HCW (p=0.008), and TNFα+ CD4 T cell responses were elevated in HD (p=0.01). In contrast to CD4 T cells, S-specific CD8 T cell responses were quantitatively reduced in HD compared to HCW after each dose (V1: p<0.001; V2: p<0.001).

**Conclusion:** People on HD develop poor B cell and CD8 T cell responses after SARS-CoV-2 mRNA vaccination. These defects are associated with a skewed differentiation of vaccine-specific CD4 T cells toward CXCR3+ and TNFα+ Th1-like profiles, and probable altered crosstalk between Thelper and B cells. Further study is needed to determine if impaired B and T cell vaccine immunity in addition to defective antibody responses increases vulnerability of HD patients to breakthrough COVID-19 infection.

## 295 ANTIBODY RESPONSE TO SARS-CoV-2 VACCINES AND IMMUNODEFICIENCY: A RANDOMIZED TRIAL

**Frédérique Chammartin**[1], Benjamin Speich[1], Irene A. Abela[2], Patrizia Amico[1], Marcel Stöckle[1], Anna L. Eichenberger[3], Macé M. Schuurmans[2], Thomas Müller[2], Michael Tamm[1], Huldrych F. Günthard[2], Michael T. Koller[1], Alexandra Trkola[2], Matthias Briel[1], Katharina Kusejko[2], Heiner C. Bucher[1]

*[1]University Hospital Basel, Basel, Switzerland, [2]University Hospital Zurich, Zurich, Switzerland, [3]University of Bern, Bern, Switzerland*

**Background:** Since January 2021, the two in Switzerland approved severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines tozinameran (Pfizer/Biontech) and elasomeran (Moderna) have been used to vaccinate the Swiss population. These vaccines were found to be safe in licensing trials with excellent efficacy of 95% and 94% in terms of preventing COVID-19 illness 14 days after the second vaccination. However, randomized evidence on the comparative effectiveness of both vaccines in immunocompromised patients is currently lacking.

**Methods:** We conducted a parallel, two-arm (allocation 1:1) open-label, non-inferiority randomized clinical trial (RCT) nested into the Swiss HIV Cohort Study (SHCS) and the Swiss Transplant Cohort Study (STCS). Patients living with HIV and solid organ transplant recipients (i.e. lung and kidney) from these cohorts were randomized to receive either tozinameran or elasomeran. The primary endpoint was an antibody response to SARS-CoV-2 spike (S1) protein receptor binding domain using Elecsys® Anti-SARS-CoV-2 S assay from Roche (binary, cut-off ≥0.8 Units/ml) 12 weeks after first vaccination (8 weeks after second vaccination). Secondary outcomes were immune response measured with the Antibody CORonavirus Assay (ABCORA), clinical and safety outcomes.

**Results:** A total of 430 patients were randomized and 412 were included in the intention-to-treat analysis (341 HIV patients and 71 solid organ transplant recipients). Antibody response was for elasomeran 92.1% (95% CI 88.4-95.8%; 186/202) and for tozinameran 94.3% (95% CI 91.2-97.4%; 198/210; difference: -2.2%; 95% CI -7.1- 2.7%), fulfilling non-inferiority of elasomeran. Overall, neutralization activity to SARS-CoV-2 Wuhan HU-1 strain was estimated to 96.5% (95% CI 94.5-98.4%) in HIV patients and 21.1% (95% CI 11.6-30.6%) in solid organ transplant recipients. 5 SARS-CoV-2 infections occurred (3 elasomeran; 2 tozinameran) and 18 serious adverse event occurred (9 elasomeran; 9 tozinameran).

**Conclusion:** In immunocompromised patients the antibody response of elasomeran was comparable to tozinameran. People living with HIV had in general a sufficient immune response while a high proportion of transplant recipients had no immune response. Nearly 80% of patients with solid organ transplant have not developed neutralizing activity and need booster vaccination.

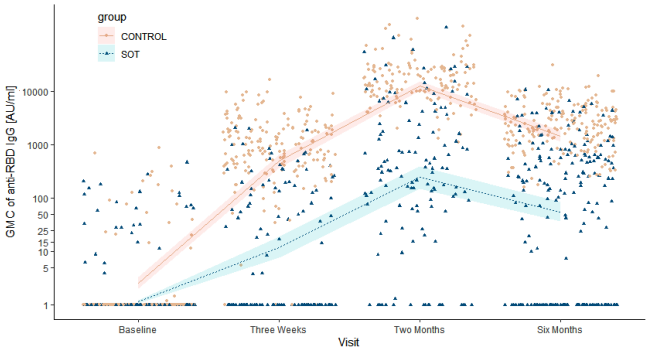
## 296 ANTIBODIES IN SOLID ORGAN TRANSPLANT RECIPIENTS 6 MONTHS AFTER BNT162b2 VACCINATION

New Investigator Scholar

**Sebastian Hamm**[1], Dina Leth Møller[1], Laura Pérez-Alós[1], Rasmus Bo Hasselbalch[2], Zitta Barrella Harboe[1], Ruth Frikke-Schmidt[1], Sisse R. Ostrowski[1], Michael Perch[1], Søren Schwartz Sørensen[1], Allan Rasmussen[1], Henning Bundgaard[1], Peter Garred[1], Kasper Karmark Iversen[2], Susanne D. Nielsen[1]

*[1]Rigshospitalet, Copenhagen, Denmark, [2]Herlev and Gentofte Hospital, Copenhagen, Denmark*

**Background:** Previous studies have shown an inferior response to mRNA SARS-CoV-2 vaccination in solid organ transplant (SOT) recipients up to four months after vaccination. We examined the development in anti-receptor binding domain (RBD) IgG after two doses of BNT162b2 in SOT recipients six months after vaccination compared to immunocompetent controls.
**Methods:** in 200 SOT recipients and 200 age- and sex-matched controls, we measured immunogenicity of two doses of BNT162b2 vaccine up to 6 months after vaccination. An in-house enzyme-linked immunosorbent assay (ELISA) based system was used to measure concentrations of anti-receptor binding domain (RBD) IgG. Neutralizing capacity of antibodies was estimated using an in-house ELISA based pseudo-neutralization assay. Presence of anti-SARS-CoV-2 nucleocapsid (N) antibodies was assessed using an electrochemiluminescence based kit from Roche diagnostics. Presence of N-antibodies was used as evidence of previous natural infection. In a subset of participants an interferon-gamma releasing assay was used to assess T-cell responses.
**Results:** SOT recipients and controls demonstrated an increase in anti-RBD IgG after both first and second dose of BNT162b2. Six months after the first dose, GMC of anti-RBD IgG declined in both groups but remained higher in controls (55.85 AU/mL, 95% CI 36.95-83.33 vs. 1448.94 AU/mL, 95% CI 1139.43-1799.48). Furthermore, more controls had a cellular response six months after vaccination (13.1% of SOT recipients vs. 59.4% of controls, p<0.001). We found increasing age (RR 1.23 pr year, 95% CI 1.11-1.35, p<0.001), being within one year of transplantation (RR 1.55, 95% CI 1.30-1.85, p<0.001), use of mycophenolate (RR 1.53, 95% CI 1.18-1.99 p=0.001), kidney transplanation (RR 1.70, 95% CI 1.25-2.30, p=0.001), lung-transplantation (RR 1.63, 95% CI 1.16-2.29, p=0.005) and cancer comorbidity (RR 1.52, 95% CI 1.26-1.82, p <0.001) to be significantly associated with humoral non- response.
**Conclusion:** Humoral and cellular responses to two doses of BNT162b2 are inferior in SOT recipients compared to controls. Furthermore, anti-RBD concentration decline 6 months after first vaccine dose. Further investigations of clinical significance of anti-RBD IgG concentration and vaccine non-response is warranted to optimize the timing and use of booster vaccines. Multiple risk factors for non-response were identified and may help identify SOT recipients at high risk of vaccine non-response.




## 297 HUMORAL RESPONSE TO SARS-CoV-2 mRNA VACCINE IN HEART TRANSPLANT RECIPIENTS

**Valentine M. Ferré**[1], Zohra Brouk[2], Heloïse Flament[3], Caroline Kernéis[2], Charlotte Charpentier[1], Vania Da Silva[2], Constance Verdonk[2], Eric Vicaut[4], Luc De Chaisemartin[5], Diane Descamps[1], Nadhira Houhou-Fidouh[2], Richard Dorent[2]
*[1]Paris University, INSERM U1137 IAME, Paris, France, [2]Assistance Publique - Hôpitaux de Paris, Bichat-Claude Bernard Hospital, Paris, France, [3]Paris University, INSERM U1149 CRI, Paris, France, [4]Paris University, Paris, France, [5]Paris Saclay University, INSERM UMR996, Paris, France*

**Background:** Recent studies reported poor to moderate humoral response after two vaccine doses in heart transplant recipients (HTR). Currently, French healthcare authorities recommend 2 and 3 vaccine injections for transplant recipients with and without prior SARS-CoV-2 infection, respectively. This study aimed to evaluate level and durability of humoral immunity with this vaccination strategy.
**Methods:** This single-center cohort study included HTR followed at Paris Bichat hospital between January 2020 and September 2021. Analyses were performed using automated immunoassays (Abbot) to quantify anti-spike IgG (cut-off ≥ 7.1 BAU/mL) and anti-nucleocapsid IgG (cut-off index > 0.49), respectively. Categorical variables were described as number (%) and continuous variables with median (IQR).
**Results:** A total of 181 HTR (75.7% males, age 58 y [47-66]) transplanted between June 1990 and June 2021, with cardiomyopathy (n=95), coronary artery disease (n=61), valvular cardiomyopathy (n=19) or other transplant indications were included. Median time from transplantation to first vaccine dose was 4.2 y [1.8-6.6]. 143 HTR (79%) had no SARS-CoV-2 infection history (HTRn) and 38 (21%) contracted the infection (HTRi) (56% before and 42% after vaccination initiation). After 2 vaccine injections, anti-S IgG seroconversion was observed for only 16% (n=12/76) of HTRn. Overall, anti-S IgG titers were lower in HTRn than in HTRi (0.5 [0.2-2.6] vs 578 [1.4–4449] BAU/mL, respectively, p=0.0001). The 3rd vaccine dose enabled to obtain 42% (n=33/72) of seroconversion among HTRn with median anti-S titers of 3.2 BAU/mL [0.4-35.0]. Only half seroconverters HTRn reached the 260 BAU/mL cut-off chosen by French authorities to define vaccination efficacy. Interestingly, these patients seem to have a sustained humoral response 4 months after the 3rd dose.
**Conclusion:** This study gives new insights on the effect of the 3rd vaccine dose in HTR with low rate of seroconversion and low titers of anti-S IgG but sustained humoral response when seroconversion occurs. Studies on vaccine efficacy against SARS-CoV-2 variants and cell-mediated immune response in this cohort are ongoing.

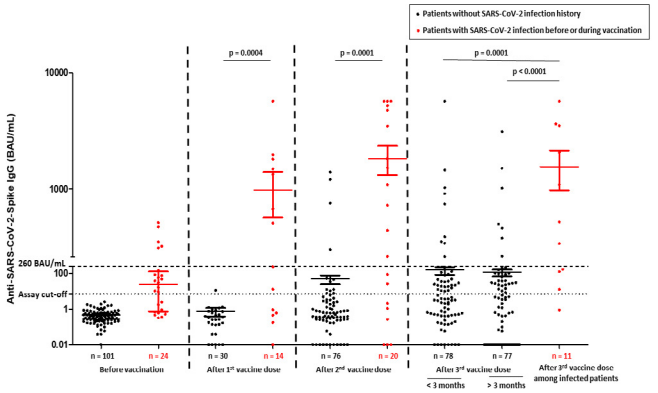



Figure 1: Humoral response of heart transplant recipients evaluated by anti-RBD of SARS-CoV-2 S1 subunit IgG titers (BAU/mL) depending on prior SARS-CoV-2 infection status at different point of vaccination: before vaccination, after the first vaccine dose (28 days in median [IQR=26-34]), after two vaccine doses (49 days [29-63]), within 3 months after the third dose (36 days [28-53]) and more than 3 months after the third vaccine dose (121 days [101-129]).

## 298 IMMUNE PARAMETERS ASSOCIATED WITH LOWER SARS-CoV-2 VACCINATION RESPONSE IN OLD PEOPLE

New Investigator Scholar

**Joana Vitalle Andrade**[1], Alberto L. Perez-Gomez[1], Maria Reyes Jimenez Leon[1], Carmen Gasca-Capote[1], Sara Bachiller[1], Francisco José Ostos[1], Inmaculada Rivas-Jeremias[2], María del Mar Silva-Sánchez[2], Anabel Ruiz-Mateos[1], Luis Fernando López Cortés[2], Mohammed Rafii-El-Idrissi Benhnia[1], Ezequiel Ruiz-Mateos[1]
*[1]Institute of Biomedicine of Seville, Sevilla, Spain, [2]Hospital Universitario Virgen del Rocio, Sevilla, Spain*

**Background:** The number of cases of SARS-CoV-2 infection after BNT162b2 mRNA vaccination is significantly higher in elderly people, which has been associated to lower frequencies of SARS-CoV-2 neutralizing antibodies. Our objective was to investigate the differences in the cellular response in old and young people after the SARS-CoV-2 vaccination.
**Methods:** Young (24-53 years, n=20) and old (70-76 years, n=20) healthy subjects vaccinated with BNT162b2 SARS-CoV-2 mRNA vaccine were studied before vaccination, two weeks after the first dose and two months after the second dose. SARS-CoV-2 (spike) specific T cell response, TLR-4 dependent monocyte response and TLR-3 dependent myeloid dendritic cell (DC) response and DC, monocyte and T-cell immunophenotype, were studied by multiparametric flow cytometry. TLR-9 dependent interferon-α (IFNα) production by PBMCs was measured by ELISA and thymic function assayed by sj/β TREC ratio using droplet digital PCR.
**Results:** The SARS-CoV-2 specific T cell response was lower and less polyfunctional in old people. Most of the differences in CD4+ and CD8+ T cell subsets were found in degranulation (CD107a), cytokine (IFN-γ) and cytotoxic (perforin) profile (eg, Memory CD8+ perforin+; p=0.0016). The lower SARS-CoV-2 specific T cell response was associated with lower thymic function levels (eg, Memory CD4+ perforin+, r=0.631; p=0.0001). The vaccination induced a higher activation and proliferation (eg, CM CD4 HLA-DR+ p=0.002, Ki67+ p=0.019) of T cells in young people than in old ones, in addition to a higher

level of homing makers to different tissues and inflammatory sites (eg, CD1c mDC integrin β7+ p=0.001, intermediate monocytes CCR2+ p=0.0003) in DCs and monocytes. Moreover, after the vaccination, old subjects showed a higher production of proinflammatory cytokines by monocytes in response to LPS (eg, IL6+; p=0.015), while young people showed a higher production of IFNα by plasmacytoid DCs after CpG-A stimulation (p=0.0009).
**Conclusion:** The magnitude and polyfunctionality of SARS-CoV-2 specific T cell response is lower in old people, associated to a lower thymic function. In old people, the vaccination induced less immune activation and homing and the myeloid TLR-dependent response is directed towards a proinflammatory response, while in young people prevails IFNα production, related to a more effective antiviral response. These results support the additional boosting strategies in this vulnerable population.

## 299 DUAL MONOCLONAL ANTIBODIES IN COVID-19 PATIENTS: CLINICAL AND VIROLOGICAL EFFICACY

**Valentine M. Ferré** [1], Nathan Peiffer-Smadja[2], Laura Kramer[3], Aïcha Kanté[4], Margaux Debarge[3], Christophe Choquet[5], Romain Coppée[6], Donia Bouzid[7], Jonathan Messika[8], Jennifer Le Grand[3], Michael Thy[9], Solen Kernéis[10], Diane Descamps[1], Benoît Visseaux[1], Jade Ghosn[2]
*[1]Paris University, INSERM U1137 IAME; Assistance Publique - Hôpitaux de Paris, Virology Department, Bichat-Claude Bernard Hospital, Paris, France, [2]Paris University, INSERM U1137 IAME; Assistance Publique - Hôpitaux de Paris, Infectious Disease Department, Bichat-Claude Bernard Hospital, Paris, France, [3]Assistance Publique - Hôpitaux de Paris, Pharmacy Department, Bichat-Claude Bernard Hospital, Paris, France, [4]Infectious Disease Department, Bichat-Claude Bernard Hospital, Assistance Publique - Hôpitaux de Paris, Paris, France, [5]Assistance Publique - Hôpitaux de Paris, Emergency Department, Bichat-Claude Bernard Hospital, Paris, France, [6]Paris University, INSERM U1137 IAME, Paris, France, [7]Paris University, INSERM U1137 IAME; Assistance Publique - Hôpitaux de Paris, Emergency Department, Bichat-Claude Bernard Hospital, Paris, France, [8]Paris University, INSERM U1152 PHERE; Assistance Publique - Hôpitaux de Paris, Pneumology Department, Bichat-Claude Bernard Hospital, Paris, France, [9]Assistance Publique - Hôpitaux de Paris, Infectious Disease Department, Bichat-Claude Bernard Hospital, Paris, France, [10]Paris University, INSERM U1137 IAME; Assistance Publique - Hôpitaux de Paris, Prevention and Control of Infection Team, Bichat-Claude Bernard Hospital, Paris, France*

**Background:** An emergency use authorization was issued in March 2021 for two combinations of monoclonal antibodies (MAbs) for SARS-CoV-2 infected patients at high risk of severe COVID-19. We performed a cohort study of patients receiving early treatment with Bamlanivimab/Etesevimab (B/E) or Casirivimab/Imdevimab (C/I) in a Paris university hospital.
**Methods:** All patients receiving a MAbs therapy from March to July 2021 were included. Prescriptions were systematically advised by a multidisciplinary team. Both MAbs dual therapies were used up to May 12th, then only C/I due to local emergence of Delta variant. Nasopharyngeal swabs (NPS) were performed at diagnosis and 7 days after infusion. Additional NPS were collected for hospitalized patients at day 3 and during follow-up until negative RT-PCR or patients discharge. Viral sequencing was carried out and viral mutations were retained if present at more than 20% of viral subpopulations.
**Results:** Overall, 66 patients (19 ambulatory) received a MAbs dual therapy for a documented SARS-CoV-2 asymptomatic infection or within 5 days after symptoms onset. Patients had a median age of 67 years [IQR=41-75], 53% were male, 30 (45%) were receiving immunosuppressive treatment (17 being solid organ recipients), 8 (12%) had chronic respiratory insufficiency, and 6 (9%) were receiving chemotherapy. Regarding variants, 82% were Alpha, 5% Delta and 13% other variants. 8 patients (12%) died (6 treated with B/E and two with C/I). Five deaths were related to COVID-19 worsening and three were unrelated. Among the surviving patients, 42 (64%) did not require any oxygen and 16 (24%) required low-flow oxygen. No severe adverse event related to MAbs occurred. A slower viral decay was observed among patients receiving B/E than C/I, with 17/29 and 5/13 having <30 Ct at day 7 post-infusion (p=0.3), respectively, and 9/14 and 1/8 at day 14 (p=0.03). Different Spike mutations emergence were observed including Q493R in 7 patients and E484K in 2 patients, all infected with an Alpha variant, and detected from 6 to 18 days after MAbs infusion. Among the 9 mutations, 8 occurred after B/E infusion and one Q493R occurred after C/I infusions.
**Conclusion:** We described safety and efficacy of early MAbs therapies administration in a cohort of 66 patients at risk of severe COVID-19. Emergence of mutations were observed under both therapies, with increased frequency under B/E. Further studies including patients infected by Delta variant and receiving C/I infusion are ongoing.

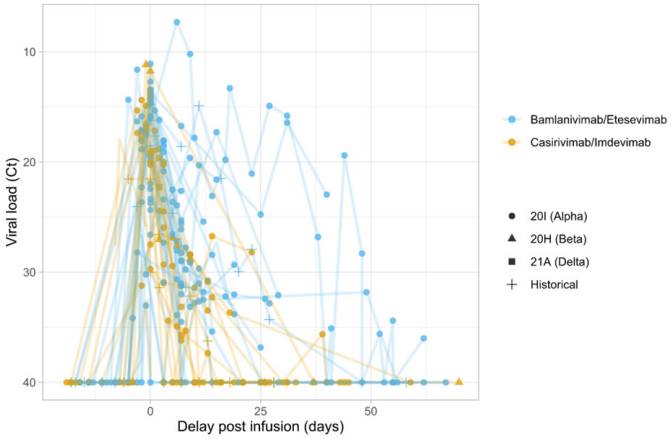
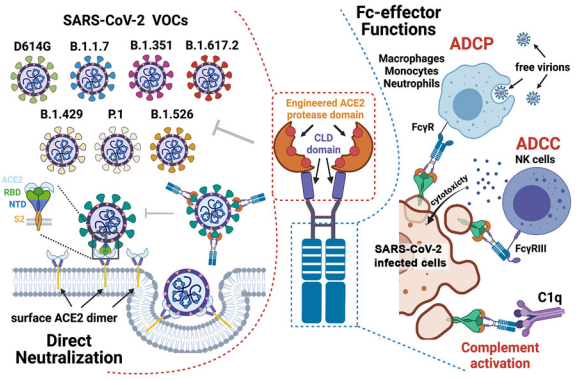



**Figure.** Viral load evolution of patients at high risk of severe COVID-19 treated with a dual monoclonal therapy, according to the dual therapy used and the viral variants. Viral loads are expressed according to Ct value obtained by RT-PCR from nasopharyngeal swabs.

## 300 IN VIVO EFFICACY OF ENGINEERED ACE2-Fc IN PREVENTING LETHAL SARS-CoV-2 INFECTION

**Yaozong Chen**[1], Lulu Sun[2], Irfan Ullah[3], Guillaume Beaudoin-Bussières[4], Andrew Hederman[5], William D. Tolbert[1], Rebekah Sherbum[1], Dung N. Nguyen[1], Priti Kumar[3], Margaret E. Ackerman[5], Walther Mothes[3], Andrés Finzi[4], Pradeep D. Uchil[3], Frank J. Gonzalez[2], Marzena Pazgier[1]
*[1]Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [2]National Cancer Institute, Bethesda, MD, USA, [3]Yale University, New Haven, CT, USA, [4]Centre de Recherche du CHUM, Montreal, Canada, [5]Dartmouth College, Hanover, NH, USA*

**Background:** Soluble Angiotensin Converting Enzyme 2 (ACE2) constitutes an attractive therapeutic candidate with natural resistance to viral escape. To date, ACE2-Fcs, dimeric forms of soluble ACE2, were mostly tested as robust SARS-CoV-2 neutralizers but their potential as antiviral agents capable of Fc-effector functions is largely unknown and has not been tested for effectiveness in vivo, in any model of SARS-CoV2 infection.
**Methods:** We used structure-guided design to select ACE2 mutations that improve SARS-CoV-2 spike (S) affinity and remove angiotensin enzymatic activity. ACE2-Fc variants were engineered into a human IgG1 or IgG3 backbone and produced in mammalian HEK293 cells. S binding was tested by ELISA and surface plasmon resonance (SPR). Mutational effects were validated by X-Ray crystallography. Neutralization activities were measured against SARS-CoV-2 variants of concern (VOCs) using an in vitro pseudovirus (PsV) assay and dynamic bioluminescence imaging (BLI). Antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) were also quantified using established methods (1, 2). A K18-hACE2 transgenic mouse model challenged by lethal SARS-CoV-2 nLuc infection (3) was used for in vivo evaluation of prophylactic and therapeutic administration of engineered ACE2-Fcs, as monitored by dynamic BLI.
**Results:** Our lead variant, ACE2740 LFMYQY2HA-Fc GASDALIE, increased RBD binding by ~7-13 fold as compared to wild type, cross-neutralized SARS-CoV-2 VOCs with an $IC_{50}$ range of 0.23-2.06 nM and mediated robust ADCC and ADCP in vitro. When tested in humanized K18-hACE2 mice, in either a prophylatic or a multi-dosage therapeutic setting, our lead ACE2-Fc variant provided protection from lethal SARS-CoV-2 infection. Our studies in K18-hACE2 mouse model revealed that efficient in vivo efficacy of ACE2-Fcs under prophylaxis or therapeutic settings required Fc-effector functions in addition to neutralization.
**Conclusion:** Our data confirm the utility of engineered ACE2-Fcs as valuable SARS-CoV-2 antivirals and demonstrate that the efficient ACE2-Fc therapeutic activity required both neutralization and Fc-effector functions.




## 301 A FC-ENHANCED NON-NEUTRALIZING ANTIBODY DELAYS SARS-CoV-2–INDUCED DEATH IN MICE

**Guillaume Beaudoin-Bussières**[1], Yaozong Chen[2], Irfan Ullah[3], Jérémie Prévost[1], William D. Tolbert[2], Kelly Symmes[3], Shilei Ding[1], Mehdi Benlarbi[1], Fei Zhou[4], Edwin Pozharski[5], Priti Kumar[3], Walther Mothes[3], Pradeep D. Uchil[3], Marzena Pazgier[2], Andrés Finzi[1]

*[1]Centre de Recherche du CHUM, Montreal, Canada, [2]Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [3]Yale University, New Haven, CT, USA, [4]National Institutes of Health, Bethesda, MD, USA, [5]University of Maryland, Baltimore, MD, USA*

**Background:** Both neutralizing activity and Fc-mediated effector functions of antibodies are believed to contribute to protection against SARS-CoV-2. However, it is unclear if antibody effector functions alone could protect against SARS-CoV-2 infection.

**Methods:** We isolated CV3-13 from a convalescent individual with potent Fc-mediated effector functions. Neutralization capacity of this antibody was measured by both a pseudovirus neutralization assay and an authentic virus microneutralization assay. We mutated the Fc-portion of CV3-13 to enhance (GASDALIE) or reduce (LALA) its capacity to mediate antibody dependant cellular cytotoxicity (ADCC). Structural analysis of CV3-13 was done by cryo-EM to characterize its epitope and its angle of approach. Finally, CV3-13 and CV3-13 GASDALIE were used in vivo in a K18-hACE2 transgenic mouse model challenged with SARS-CoV-2-nLuc to see if they altered viral replication and/or contributed to protection against SARS-CoV-2.

**Results:** While CV3-13 did not neutralize SARS-CoV-2, it demonstrated nanomolar affinity towards the SARS-CoV-2 Spike and mediated strong ADCC. The cryo-EM structure of CV3-13 in complex with the SARS-CoV-2 Spike revealed that the antibody bound to a novel NTD epitope that partially overlapped with a frequently mutated NTD supersite in SARS-CoV-2 variants. Interestingly, this angle of approach was not observed for previously described NTD-directed antibodies. While CV3-13 did not alter the replication dynamics of SARS-CoV-2 in a K18-hACE2 transgenic mouse model, a Fc-enhanced CV3-13 significantly delayed neuroinvasion and death in prophylactic settings.

**Conclusion:** CV3-13 represents a new class of non-neutralizing NTD-directed mAbs that can mediate Fc-effector functions both in vitro and in vivo. While effector functions alone did not protect K18-hACE2 mice from SARS-CoV-2-nLuc challenge, our data indicate that along with neutralization, additional antibody properties including Fc-mediated effector functions contribute to limiting viral spread and aid in fighting SARS-CoV-2 infection.

## 302 REAL-LIFE USE OF HIGH-DOSE ANAKINRA IN COVID-19 PATIENTS TREATED WITH REMDESIVIR

New Investigator Scholar

**Roberta Monardo**[1], Andrea Mastrangelo[1], Laura Galli[2], Alessandro Tomelleri[2], Vincenzo Spagnuolo[2], Chiara Oltolini[2], Giacomo Ponta[1], Corrado Campochiaro[2], Lorenzo Dagna[1], Giulio Cavalli[1], Fabio Ciceri[1], Paola Cinque[2], Paolo Scarpellini[2], Antonella Castagna[1], Marco Ripa[1]

*[1]San Raffaele Vita-Salute University, Milan, Italy, [2]San Raffaele Scientific Institute, Milan, Italy*

**Background:** COVID-19 is characterized by a dysregulated inflammatory response associated with disease severity, poor prognosis and death. The aim of this study was to describe the real-life use of high-dose anakinra (ANK, a recombinant IL-1 receptor antagonist) among patients with COVID-19 who received remdesivir (REM).

**Methods:** Cohort study including 277 patients with COVID-19 hospitalized at IRCCS San Raffaele Hospital between September 1st,2020 and February 28th, 2021; 58 patients were treated with REM+ANK and 219 patients with REM only. ANK was administered intravenously at a dose of 5mg/kg every 12 hours. Patients were treated according to available local and international guidelines; corticosteroids and anticoagulation were administered when not contraindicated. Results are described by median (IQR) or frequency (%); P-values (P) were calculated by chi-square or Fishers' exact test and Wilcoxon rank-sum test, as appropriate. Survival estimates at 28 days were calculated using Kaplan-Meier curves.

**Results:** At hospital admission (Table 1), patients treated with REM+ANK tended to be older [69 years (57-77) vs 62 years (53-75), P=0.06], had a significant lower PaO2/FiO2 [135 (91-220) vs 246 (172-299), P=0.0001], higher aspartate aminotransferase [51U/L (34-74) vs 40U/L (30-53), P=0.001], lactate dehydrogenase [405U/L (296-496) vs 334U/L (279-419), P=0.008], D-dimer [0.86mcg/mL (0.48-1.57) vs 0.67mcg/mL (0.39-1.17), P=0.048], ferritin [1167ng/mL (804-1983) vs 683ng/mL (391-1153), P<0.0001] and C-reactive protein [82mg/L (38-136) vs 58 mg/L (27-96), P=0.004), and were more frequently admitted to the Intensive Care Unit within the first 48 hours [3 (1.1%) vs 0, P=0.007). REM and ANK were started early within a median of 0 (0-2) and 1.5 days (0-3) since hospitalization, respectively. The Kaplan-Meier estimate of mortality at 28 days was 17.2% (95%CI 8.8-32.1%) in the REM+ANK group (8 deaths) and 21.4% (95%CI 13.3-33.3%) in the REM group (18 deaths; log-rank test P=0.797). Median time to death was 14 days (9-29) in the REM+ANK group vs 19 days (12-27) in the REM group (P=0.523).

**Conclusion:** Real-life use of high-dose ANK in COVID-19 patients treated with REM was reserved for subjects with severe respiratory failure and a more pronounced inflammatory status. Nevertheless, mortality at 28 days was not significantly different among patients treated with or without ANK. Further analyses are warranted to verify the impact of ANK addition to REM in patients with a hyperinflammatory profile.

| Variable | Category | Overall (n=277) | ANK+REM (n=58) | REM (n=219) | P-value |
|---|---|---|---|---|---|
| AGE years | | 65 (53 - 76) | 69 (57 - 77) | 62 (53 - 75) | 0.06 |
| Male sex | | 182 (65.7%) | 43 (74.1%) | 139 (63.5%) | 0.161 |
| PaO2/FiO2 at admission | >300 | 42 (15.2%) | 6 (10.3%) | 36 (16.4%) | 0.008 |
| | >200 - <=300 | 73 (26.4%) | 11 (19%) | 62 (28.3%) | |
| | >100 - <=200 | 50 (18.1%) | 14 (24.1%) | 36 (16.4%) | |
| | <=100 | 27 (9.7%) | 12 (20.7%) | 15 (6.8%) | |
| | Unknown | 85 (30.7%) | 15 (25.9%) | 70 (32%) | |
| Admission to ICU within 48 hours | | 3 (1.1%) | 3 (5.5%) | 0 | 0.007 |
| Alanine aminotransferase (U/L) | | 36 (22 - 54) | 41 (25 - 55) | 34.5 (21 - 53) | 0.167 |
| Aspartate aminotransferase (U/L) | | 42 (31 - 57) | 51 (34 - 74) | 40 (29.5 - 53) | 0.001 |
| Ferritin (ng/ml) | | 802 (457 - 1364) | 1167 (804 - 1983) | 683 (391 - 1153) | <0.0001 |
| Lactate dehydrogenase (U/L) | | 341 (281 - 430) | 405 (296 - 496) | 334 (279 - 419) | 0.008 |
| C reactive protein mg/L | | 62.5 (31.8 - 108) | 81.6 (38.4 - 136) | 57.8 (26.8 - 96) | 0.004 |
| PT (second) | | 13.8 (13.2 - 14.7) | 13.85 (13.2 - 14.7) | 13.8 (13.1 - 14.7) | 0.51 |
| D-dimer (mcg/ml) | | 0.74 (0.4 - 1.32) | 0.86 (0.48 - 1.57) | 0.67 (0.39 - 1.17) | 0.048 |
| Lymphocyte (x10$^9$/L) | | 0.9 (0.6 - 1.2) | 0.85 (0.6 - 1.2) | 0.9 (0.7 - 1.2) | 0.203 |
| Neutrophilis (x10$^9$/L) | | 5 (3.4 - 7) | 5.3 (3.6 - 7.9) | 4.9 (3.4 - 6.7) | 0.148 |
| Duration of hospitalisation (days) | | 13 (8 - 20) | 17.5 (11 - 28) | 12 (8 - 19) | 0.0005 |

Results decribed by median (IQR) or frequency (%); P-values by chi-square or Fishers' exact test and Wilcoxon rank-sum test, as appropriate.

## 303 METHYLPREDNISOLONE PULSES IN HOSPITALIZED PATIENTS WITH SEVERE COVID-19 PNEUMONIA

New Investigator Scholar

**Giovanni Dolci**[1], Carlo Salvarani[1], Marco Massari[2], Gabriella L. Mariani[2], Massimo Costantini[2], Franco Merlo[2], Pierluigi Viale[3], Stefano Nava[3], Emanuele A. Negr[2], Chiara Barbieri[2], Luisa Savoldi[2], Mariagrazia Catanoso[2], Luca Boni[4], Nicola Facciolongo[2]

*[1]University of Modena and Reggio Emilia, Modena, Italy, [2]Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [3]Alma Mater Studiorum Università di Bologna, Bologna, Italy, [4]Azienda Ospedaliero Universitaria Careggi, Firenze, Italy*

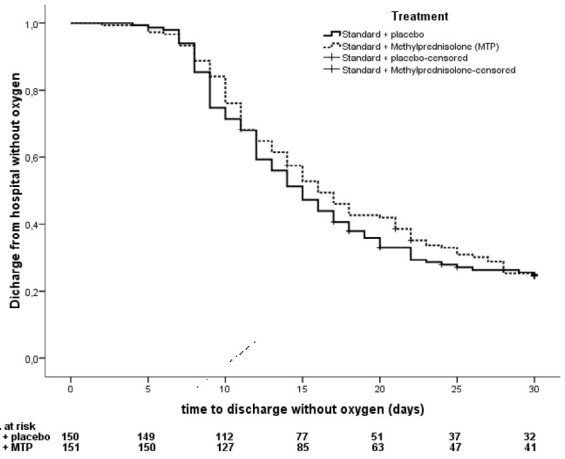
**Background:** Pulse glucocorticoid therapy (> 250 mg of prednisone equivalent per day for 1 or a few days) is used in many immuno-inflammatory diseases for its quick and strong anti-inflammatory effect in emergency situations. It was used during in Severe Acute Respiratory Syndrome epidemics with no consistent data regarding its benefits. The efficacy and safety of this therapy associated to dexamethasone in coronavirus disease 2019 (Covid-19) pneumonia are unclear.

**Methods:** We conducted a double-blind, randomized, placebo-controlled trial in hospitalized patients with COVID19-pneumonia. The study population included patients hospitalized for recent-onset Covid-19 pneumonia requiring supplemental oxygen in any delivery mode, except invasive mechanical ventilation, with PaO2/FiO2 between 100 and 300, and a C-reactive protein greater than 5 mg/dl. Patients were randomly assigned to receive 1 gram of methylprednisolone for 3 consecutive days or placebo in addition to standard dexamethasone. The primary outcome was the duration of the patient

hospitalization, calculated as the time interval between randomization and hospital discharge without the need of supplementary oxygen. All-cause mortality, survival free from invasive ventilation and safety were also evaluated. Written informed consent was obtained from each patient or from the patient's legally authorized representative if the patient was unable to provide consent.

**Results:** A total of 304 patients underwent randomization in 19 Italian sites between December 21, 2020, and March 10, 2021. Three patients retired the consent to the study one day after randomization, leaving 301 patients eligible for intention to treat analyses. 112 of 151 (74.2%) patients in the pulse methylprednisolone arm and 111 of 150 (74.0%) patients in the placebo arm were discharged from hospital without oxygen (p = 0.528) within 28 days from randomization. We did not observe any significant differences between pulse methylprednisolone and placebo arms in terms of admission to Intensive Care Unit with orotracheal intubation or death (19.9% versus 16.0% respectively; hazard ratio, 1.27; 95%CI, 0.74-2.16), or in terms of overall mortality (9.3% versus 11.3% respectively; hazard ratio, 0.82; 95%CI, 0.40-1.66). Serious adverse events occurred in 9 patients (6.0%) in the methylprednisolone pulse group and in 12 patients (8.0%) in the placebo group.

**Conclusion:** Methylprednisolone pulse therapy in addition to dexamethasone was not of benefit in patients with COVID-19 pneumonia.




Kaplan-Meier estimates of Hospital discharge without oxygen

## 304 SEX DIFFERENCES IN CYTOKINE PROFILES DURING SUPPRESSIVE ANTIRETROVIRAL THERAPY

**Christophe Vanpouille**[1], Alan Wells[2], Timothy Wilkin[3], Jyoti S. Mathad[3], Sheldon Morris[2], Leonid Margolis[1], Sara Gianella[2]

*[1]National Institute of Child Health and Human Development, Bethesda, MD, USA, [2]University of California San Diego, La Jolla, CA, USA, [3]Weill Cornell Medicine, New York, NY, USA*

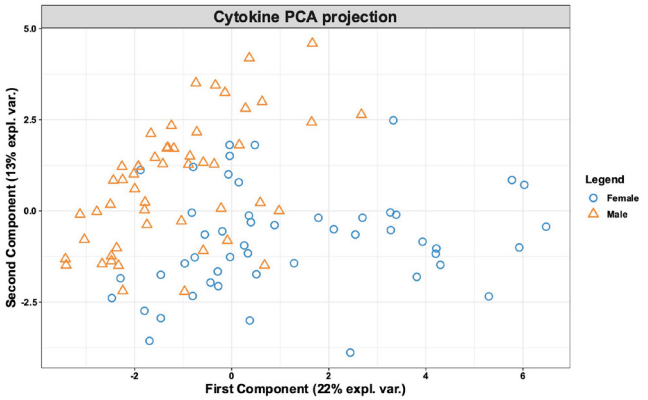
**Background:** Despite lower HIV RNA levels, women progress faster to AIDS than men. The reasons for these observations are not clear but might be a consequence of a heightened inflammatory response in women, which could also contribute to sex differences in HIV persistence.

**Methods:** We investigated sex differences in cytokine profiles by measuring the concentrations of 36 cytokine/chemokines by Luminex in blood of 50 women and 49 men (sex at birth) with chronic HIV under suppressive therapy. We initially performed a principal component analysis to see if participants clustered by sex, and then fit a PLS-DA model where we used cytokines to predict sex at birth. The significance of the difference in 9 cytokines with VIP>1 was further tested using a Wilcoxon rank-sum test for 8 continuous cytokines and Fisher's exact test for VEGF (remaining categorical cytokine, as detected versus non detected).

**Results:** Median age was 53 years for women and 46 years for men; 26 (52%) women were post-menopausal and 43 (86%) acquired HIV through heterosexual contact. All men reported sex with men as risk factor. Both groups had suppressed plasma HIV RNA. Median CD4+ T cell counts were 721 cells/µl (range: 300-1362) for women and 625 (range: 282-1149) for men. Overall, PCA analysis on cytokine profile shows distinct clustering of men (orange triangles) and women (blue circles), see Figure 1, Panel A. We were able to predict sex at birth in the PLS-DA model with an error rate of approximately 13%. We further identified 7 cytokines which were all significantly higher (or detected at a higher rate) in women compared to men. Five inflammatory chemokines, namely Gro-α, RANTES, MIP-1α, MIP-1β, IL-16, as well as the T-cell homeostatic factor IL-7 and the endothelial factor VEGF, see Figure 1, Panel B.

**Conclusion:** The observed sex-based differences in cytokines might contribute to maintain higher immune activation in women compared to men despite suppressive therapy and may explain why women progress faster to AIDS and experience more HIV-related complications. Further, increased levels of IL-7 in women suggest that homeostatic proliferation may have a differential contribution to HIV reservoir maintenance in women than men. Our study emphasizes the importance of sex-specific studies of viral pathogenesis.

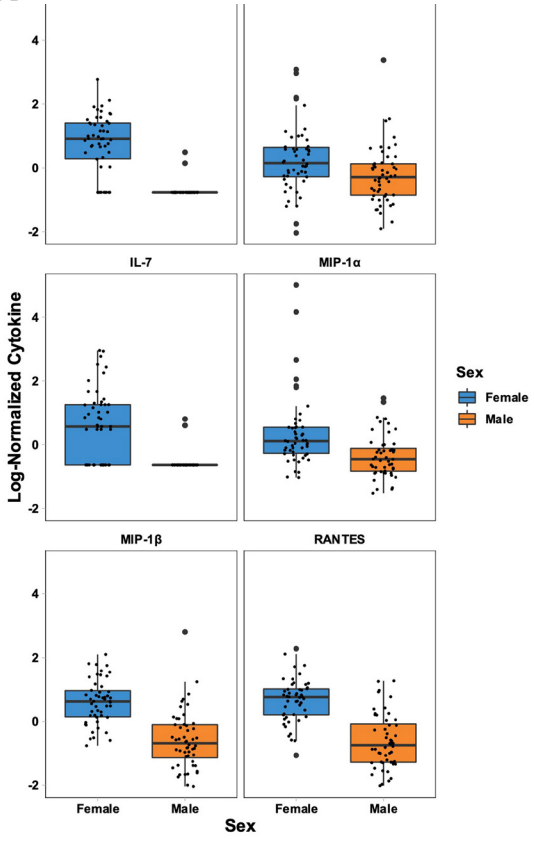
**Panel A**




**Panel A. Principal component analysis (PCA) of cytokine profiles in women compared to men with HIV on suppressive ART.** PCA analysis on cytokine profile shows distinct clustering of men (orange triangles) and women (blue circles). The first and second principal components explain 22% and 13% of the variance, respectively.

**Panel B. Effect of sex (at birth) on chemokine/cytokine in blood plasma.** Shown is the difference of the concentrations for six chemokine/cytokines ($log_{10}$ normalized) in women and men with HIV on suppressive ART. The statistical significance of 8 continuous cytokines with VIP>1 identified in the PLS-DA model were further tested by Wilcoxon Rank Sum test. Six out of 8 remained significant. The concentrations of these 6 Chemokine/cytokines were $log_{10}$-transformed and plotted as boxplots. For each cytokine and each boxplot, each point represents a participant's cytokine concentration, the box represents the interquartile range (IQR), the middle line represents the median, while the points beyond the whiskers are outliers. All chemokine/cytokines had higher concentrations in women compared to men.

**Panel B**



## 305 DOWNREGULATION OF CD155 RESULTS IN HIV-1 RESTRICTION BY KIR2DL5+ NK CELLS

**Pia Fittje**[1], Angelique Hölzemer[1], Wilfredo F. Garcia-Beltran[1], Annika Niehrs[1], Sarah Vollmers[1], Glòria Martrus[1], Christian Körner[1], Frank Kirchhoff[2], Daniel Sauter[3], Marcus Altfeld[1]
*[1]Heinrich Pette Institute, Hamburg, Germany, [2]Ulm University Medical Center, Ulm, Germany, [3]University Hospital Tübingen, Tübingen, Germany*

**Background:** Ligands for the inhibitory NK cell receptor KIR2DL5 are not well defined. CD155 has recently been shown to not only bind the activating receptor DNAM1, but to also interact with KIR2DL5. However, the functional relevance of KIR2DL5/CD155 interactions for the anti-HIV-1 activity of NK cells remained unknown. Previous studies suggested that HIV-1 decreases CD155-expression on infected cells and thereby evade immune recognition by DNAM1-positive NK cells. However, the newly described interaction between KIR2DL5 and CD155 indicates a more complex regulation of NK cell responses by CD155.
**Methods:** Binding of KIR2DL5 to CD155 was analyzed using KIR-IgG fusion construct staining of CD155-coated beads and KIR2DL5-expressing reporter cells. To unravel functional interactions between CD155 and KIR2DL5, NK cell degranulation in response to CD155-expressing target cells was assessed using primary human NK cells. To determine cell surface expression of CD155 during HIV-1 infection, primary CD4+ T cells were infected with eight different wild type HIV-1 strains or their respective Δnef mutants and CD155-expression was quantified by flow cytometry. The antiviral activity of KIR2DL5+ NK cells was determined by viral inhibition following co-cultivation of NK cells with HIV-1 wild type or Δnef mutant infected cells.
**Results:** We observed binding of KIR2DL5 to CD155 and activation of KIR2DL5+ reporter cells after co-incubation with CD155-coated beads ($p < 0.01$). Primary human KIR2DL5+ NK cells displayed lower degranulation levels after incubation with CD155+ target cells compared to CD155- target cells ($p < 0.01$). NK cell inhibition was abrogated by blocking the interaction between CD155 and KIR2DL5. Furthermore, all tested primary transmitted-founder and cell line-adapted HIV-1 strains downregulated CD155 on the surface of infected primary CD4+ T cells in a Nef-dependent manner ($p < 0.01$). Co-culture of infected CD4+ T cells with NK cells revealed increased viral inhibition by KIR2DL5+ NK cells of wild-type versus Nef-deficient viruses ($p < 0.01$).
**Conclusion:** These data show that CD155 serves as a functional ligand for the inhibitory NK cell receptor KIR2DL5, suppressing the antiviral activity of KIR2DL5+ NK cells. CD155 is downregulated by HIV-1 Nef to counteract activating NK cell receptors, such as DNAM-1. However, HIV-1-mediated downregulation of CD155 renders infected cells more vulnerable to recognition by KIR2DL5+ NK cells.

## 306 THE ROLE OF ADAPTIVE NK CELLS DURING ACUTE HIV-1 INFECTION WITH DIFFERENT SUBTYPES

**Aljawharah Alrubayyi**[1], Amin Hassan[2], Jonathan Hare[3], Jill Gilmour[4], Joakim Esbjörnsson[5], Eduard Sanders[2], Sarah Rowland-Jones[1], Dimitra Peppa[6]
*[1]University of Oxford, Oxford, UK, [2]KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya, [3]International AIDS Vaccine Initiative Human Immunology Lab, London, UK, [4]Imperial College London, London, UK, [5]Lund University, Lund, Sweden, [6]University College London, London, UK*

**Background:** Understanding the early immune response to HIV-1 infection represents a unique opportunity for the identification of novel targets for prophylactic/therapeutic approaches. Natural Killer (NK) cells are an important component of innate immunity that can modulate the pathogenesis of acute HIV-1 infection (AHI). However, the role of NK cells in mediating early host defence against infection with different HIV-1 subtypes, and clinical outcomes, remains poorly understood. Here, we studied the early imprinting effects of different HIV-1 subtypes and pro-inflammatory environment on the NK cell compartment in a unique cohort with AHI.
**Methods:** Participants with AHI were sampled longitudinally in different sub-Saharan African sites under "IAVI protocol C" (n=25 subtype A, n=17 subtype C, n=7 subtype D). The median estimated days post infection for subtype A and non-subtype A was 32 and 35 days respectively (visit 1), and 95 and 92 days (visit 2). Multiparameter flow cytometry was used for the phenotypic characterisation. NK cell ADCC responses were determined against antibody coated Raji cells. The metabolic profile was assessed by a Seahorse technology. Soluble markers were measured using multiplexed assays.The Mann–Whitney U, Wilcoxon-test, and Spearman tests were used in the analysis.
**Results:** NK cell subsets with adaptive/memory features expand during AHI with subtype A compared to non-A (visit 1 p=0.008, visit 2 p=0.005). This adaptive NK cell signature was delineated by lower expression of the transcription factor PLZF and was further enriched by higher expression of the activating receptor NKG2C and lower expression of the signalling molecule FcεRγ. Individuals with high frequency of adaptive NK cells exhibited higher levels of IL-12p70 (p=0.03). Increased frequencies of adaptive NK cells were associated with lower HIV viral load (p=0.017) and higher CD4 T cell counts (>500). These phenotypic attributes were accompanied by enhanced NK cell ADCC capacity and higher IFN-γ (p=002) and TNF-α (p=0.0165) production in subtype A versus non-A. Notably, NK cell IFN-γ production correlated inversely with HIV-1 viral load (r=-0.343, p=0.03). The enhanced functionality of NK cells was reflected in their superior capacity for oxidative phosphorylation (p=0.035).
**Conclusion:** These data suggest that specific NK cell subsets could confer better HIV-1 control, highlighting their potential role as a prognostic marker and as a new target for the development of novel immunotherapeutic and 'cure' strategies.

## 307 CHARACTERIZATION OF NK CELLS IN ELITE CONTROLLERS LOSING HIV CONTROL

**Nerea Sánchez-Gaona**[1], Ana Gallego Cortés[1], Antonio Astorga Gamaza[1], Norma Rallón[2], José M. Benito[2], Vicenç Falcó[3], Meritxell Genescà[1], Maria José Buzón[1]
*[1]Vall d'Hebron Research Institute, Barcelona, Spain, [2]Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain, [3]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain*

**Background:** HIV-infected elite controllers (EC) are defined as individuals with undetectable viral load in the absence of treatment. Consequently, the nature of their effector immune response is of considerable interest. In this study, using samples from 3 different cohorts of EC: 5-20 years long-term (LTEC); 1-4 years short-term (STEC) and LTEC losing control (LTEC-LC), we asked if phenotypical or functional signatures of NK cells would define the loss of control.
**Methods:** PBMC samples from n=36 EC (n=16 LTEC; n=8 STEC and n=12 LTEC-LC) and n=15 healthy donors (HD) were included in the study. Flow cytometry was used for the phenotypic studies and included the markers CD57, CD56, Nkp30, NKG2C, NKG2A, CD16, CXCR3, CD158b, KLRG1, CD69 and HLA-DR. Activation studies were performed after co-culturing isolated NK cells with the K562 cell line in the presence of IL-15 for 4h. IFNg and CD107a production was measured by flow cytometry. Antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism was assessed after co-culturing NK cells with the chronically-infected cell line ACH-2.
**Results:** All three cohorts exhibited a significant decrease in the expression of the activating receptor Nkp30 by NK memory-like cells compared to HD (pLTEC<0.0005, pLTEC-LC<0.05,and pSTEC<0.005). LTEC-LC patients showed a decreased proportion of NK memory-like cells (NKG2C+CD56dimCD16high), compared to LTEC patients (p<0.01). Within the CD56dimCD16high NK population, LTEC-LC presented a significantly higher expression of the inhibitory receptor NKG2A (pLTEC<0.05 and pSTEC<0.005), and the functional markers IFNg and CD107a, being these signatures more evident within the memory-like NK cell population (pLTEC<0.05). Furthermore, NK cells from LTEC-LC patients showed significantly lower ADCC activity against HIV-expressing cells (pHD<0.005, pLTEC<0.05 and pSTEC<0.05, all compared with LTEC-LC).
**Conclusion:** Our study identifies phenotypical and functional differences in the NK cell repertoire in different cohorts of EC. The loss of a memory-like NK compartment, together with an increased basal activation state in NKG2C+ NK cells, and a decrease in the ADCC response against HIV-infected cells might contribute to the loss of immune-mediated control in LTEC. Further studying these mechanisms will help design novel therapeutic strategies to eliminate HIV infection.

## 308 TGF-β SIGNALING PATHWAY SHAPES ADAPTIVE IMMUNITY IN EARLY SARS-CoV-2 INFECTION

**Yulong Wei**[1], Jack A. Collora[1], Runxia Liu[1], Jon Klein[1], Carolina Lucas[1], Akiko Iwasaki[1], Ya-Chi Ho[1]
*[1]Yale University, New Haven, CT, USA*

**Background:** SARS-CoV-2 induces cytokine response dysregulation and immune dysfunction. What remains unclear is how cytokine signaling shapes immune responses during early SARS-CoV-2 infection when adaptive immunity is developing. Our goal is to identify immune pathways that shape

the early development of adaptive immune responses in COVID-19 patients. We performed paired single-cell transcriptomic and epigenomic profiling at two time-points of early SARS-CoV-2 infection to determine immune signatures of acute infection and epigenetic drivers that underpin immune response dynamics.

**Methods:** PBMC samples were collected from four moderate to severe COVID-19 patients at two early time-points (n = 3 for Week 1 and n = 3 for Week 2 after symptom onset, including 2 participants having paired blood sampling at both time points) and from two healthy controls (n = 2). Using paired scRNA-Seq and scATAC-Seq, we captured transcriptomic and epigenomic profiles in the same single cells to identify chromatin accessibility changes as a potential mechanism for the surge and decline of immune responses elicited during acute SARS-CoV-2 infection. Using bioinformatic approaches, we identified heterogeneous immune cell populations, modeled cell differentiation trajectories, determined dysregulated immune pathways through gene set enrichment analysis, and connected chromatin co-accessible landscapes.

**Results:** We captured transcriptomic and epigenomic profiles of 43,726 single cells and identified paired transcriptional and epigenetic landscapes in six major immune cell types: CD4+ T cells, CD8+ T cells, B cells, dendritic cells, monocytes, and NK cells. We found that early SARS-CoV-2 infection induced a surge in IL-2, IL-6, IFN-α, IFN-γ, TNF-α, and NF-κB responses at Week 1 that declined at Week 2 in adaptive immune cells (CD4+ T, CD8+ T, and B cells). In contrast, TGF-β responses surged early at Week 1 and continued to increase at Week 2 in these cells. In B cells and plasmablasts, we found early surges of IGHA1 (encoding IgA heavy chain) and SOX4 (an essential transcription factor for B cell development) expressions that correlated with expression of SMAD-dependent TGF-β signaling pathway. Further, we found a notable increase in chromatin accessibility at the SMAD binding regulatory element 150 kb upstream of SOX4 in B cells of infected patients.

**Conclusion:** Our data suggest a significant increase in TGF-β activity that instructs dynamic B cell-associated protective immunity during early SARS-CoV-2 infection.

## 309 SYSTEMATIC ANALYSIS OF INNATE IMMUNE ANTAGONISM OF SARS-CoV-2 AND ITS EVOLUTION

**Lennart Koepke**[1], Rayhane Nchioua[1], Manuel Hayn[1], Maximilian Hirschenberger[1], Annika Schundner[2], Fabian Zech[1], Susanne Klute[1], Steffen Stenger[1], Karl-Klaus Conzelmann[3], Jan Muench[1], Dorota Kmiec[1], Manfred Frick[2], Frank Kirchhoff[1], Konstantin Sparrer[1]

*[1]Ulm University Medical Center, Ulm, Germany, [2]Ulm University, Ulm, Germany, [3]Ludwig-Maximilians-Universität München, München, Germany*

**Background:** The innate immune system is a powerful anti-viral defense mechanism, which includes the interferon (IFN) system and autophagy. Thus, successful pathogens like SARS-CoV-2 need to counteract or evade these defenses to establish an infection. However, due to its ongoing, worldwide spread in the human population SARS-CoV-2 is evolving and in the meantime four variants with selection advantages (variants of concern) emerged.

**Methods:** Using expression constructs for 29 SARS-CoV-2 proteins we evaluated the impact of individual viral proteins on induction of cytokines (IFNA4, IFNB1, IRF3-signalling, NF-κB-signaling) and cytokine signaling (IFNα2, IFNβ, IFNγ, IFNλ1, IL-1α, TNFα) in luciferase reporter assays, validated by endogenous transcription factor phosphorylation analysis. We assessed the influence of SARS-CoV-2 proteins on autophagy using a flow cytometry-based system. Underlying molecular mechanisms were investigated on an endogenous level using Western blot, confocal fluorescence microscopy, and flow cytometry. In addition, we examined the susceptibility of SARS-CoV-2 including all variants of concern towards type-I, -II, and -III interferons.

**Results:** To understand how SARS-CoV-2 efficiently manipulates the host's innate immune defenses, we systematically analyzed the impact of SARS-CoV-2 encoded proteins on induction of various IFNs and pro-inflammatory cytokines, IFN signaling, and autophagy. Our results reveal the range of innate immune antagonists encoded by SARS-CoV-2 and we characterized selected molecular mechanisms employed by Nsp1 and Nsp14 to downregulate the IFN system or ORF3a and ORF7a to prevent autophagic degradation. Interestingly, our assays show that variants of concern of SARS-CoV-2 remain sensitive to type-II interferon signaling but show increased resistance towards type-I and/or type-III interferons.

**Conclusion:** SARS-CoV-2 has evolved to counteract innate immunity using several synergistic approaches but remains relatively sensitive to type-II and -III interferons. However, emerged variants of concern remain sensitive overall but are less susceptible towards IFNα2/β and IFNλ1 than early SARS-CoV-2 isolates.

## 310 DETECTION OF CIRCULATING AND AIRWAY AUTOANTIBODIES TO IFN IN SEVERE COVID-19 PATIENTS




**Federica Frasca**[1], Mirko Scordio[1], Giuseppe Oliveto[1], Leonardo Sorrentino[1], Agnese Viscido[1], Camilla Bitossi[1], Alessandra Pierangeli[1], Luigi Celani[1], Giancarlo Ceccarelli[1], Letizia Santinelli[1], Claudio M. Mastroianni[1], Gabriella D'Ettorre[1], Guido Antonelli[1], Carolina Scagnolari[1]

*[1]Sapienza University of Rome, Rome, Italy*

**Background:** Evidence suggest that critically ill COVID-19 patients have an impairment of IFN-I response. This defect in antiviral mechanisms is explained in some patients by the presence of anti IFN-alpha neutralizing autoantibodies (NAbs). However, whether NAbs fluctuate longitudinally during COVID-19, and what are their specificity toward IFN-I subtypes and consequences on the IFN response remain elusive.

**Methods:** Binding antibodies (BAbs) to IFN-alpha and IFN-beta were screened in serum samples (n=360) of COVID-19 patients using ELISA assays. All serum samples containing BAbs were processed to investigate NAbs using antiviral bioassay. Respiratory samples (n=17) were also included for the NAbs analysis. Transcript levels of IFN-alpha, IFN-beta, IFN-omega and IFN stimulated genes (ISGs) were analyzed through RT/Real Time PCR.

**Results:** Results showed that 16.94% (61/360) of COVID-19 patients had circulating BAbs against IFN-alpha and IFN-beta. Further, 21% (13/61) of critically ill subjects had NAbs with a variable titer against all the IFN-alpha subtypes (70–71680 TRU/ml) while only 1 patient had anti IFN-beta NAbs. About 70% of these serum samples showed cross reactivity to IFN-omega at different extent (27–106667 TRU/ml). Longitudinal evaluation at different time points after hospitalization indicate the persistence of high NAbs titer throughout the time. NAbs to IFN-alpha (10–20 TRU/ml) were also detected in 17.64% of respiratory samples. Patients with NAbs had severe disease and exhibited alterations in the levels of many hematological indicators [(white blood cells, neutrophils, platelets, neutrophils to lymphocytes ratio, platelets to lymphocytes ratio, D-dimer, C-reactive protein and lactate dehydrogenase; $p<0.05$)]. Transcriptomic analysis indicated that levels of IFN genes were lower in NAbs patients than in healthy donors ($p\leq0.05$). However, only the ISGs levels were reduced compared to those found in the NAbs negative patients. Of note, expression of ISGs, was abolished during hospitalization in all patients with persistent high titer of NAbs.

**Conclusion:** Our finding demonstrate that NAbs with a broad specificity to IFN-I can be found in blood and respiratory samples from severe COVID-19 patients. NAbs detection was associated with a defective IFN response and with an increased levels of markers of disease severity.

## 311 DIFFERENTIAL IFN GENES EXPRESSION IN THE UPPER AIRWAYS OF CHILDREN AND ADULTS




**Leonardo Sorrentino**[1], Federica Frasca[1], Giuseppe Oliveto[1], Mirko Scordio[1], Agnese Viscido[1], Matteo Fracella[1], Fabio Midulla[1], Raffaella Nenna[1], Gabriella D'Ettorre[1], Giancarlo Ceccarelli[1], Ombretta Turriziani[1], Massimo Gentile[1], Guido Antonelli[1], Alessandra Pierangeli[1], Carolina Scagnolari[1]

*[1]Sapienza University of Rome, Rome, Italy*

**Background:** Children generally develop a mild disease after SARS-CoV-2 infection; it has been shown (Loske J al., 2021) that higher basal expression of relevant pattern recognition receptors may result in a stronger early innate antiviral than in adults. However, how the early interferon (IFN) response differs from that in adults is not fully characterized. Hence, we aimed to investigate the expression of several IFN-related genes in nasopharyngeal (NP) cells from children and adults with asymptomatic or mild COVID-19, not requiring hospitalization.

**Methods:** Children and adults attending emergency departments (ED) of Sapienza University Hospital, to perform SARS-CoV-2 molecular tests, were enrolled from November 2020 to February 2021, after informed consent was obtained. RNA from residual NP swabs was purified and 200 ng were reverse transcribed. Gene expression of genes coding for type I and III IFNs and for the well-known markers of IFNs' activation, ISG15 and ISG56, was measured by exonuclease-based Real time PCR assays with relative quantification to the invariant gene GUS (the 2−ΔCt method).

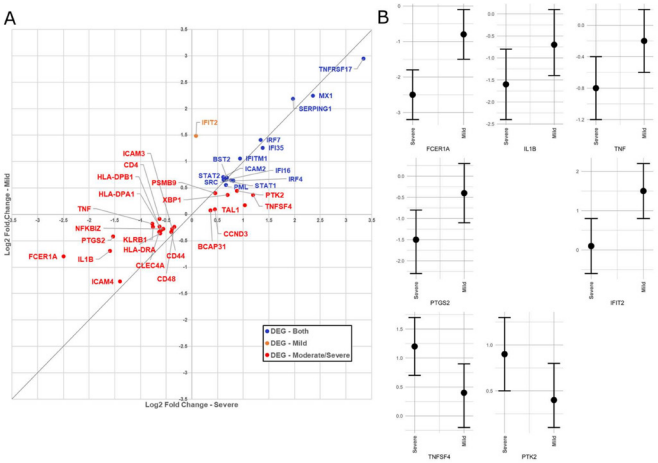
**Results:** Residual NP cells from a total of 132 children and adults were included in the study; 56 had SARS-CoV-2 positive results and 76 resulted negative. The expression of all tested genes showed a moderate significant inverse correlation with age, with the exception of ISG15. Participants were further stratified in age groups (< 16; 16-35; 36-65 years) resulting in: 25 SARS-CoV-2 negative and 26-positive children; 14 SARS-CoV-2 negative and 16-positive young adults and 37 SARS-CoV-2 negative and 14-positive adults. In SARS-CoV-2 negative samples, higher levels of all study genes were found in children, while significantly decreasing in young and elderly adults. Among SARS-CoV-2 positive samples, those from children showed significantly higher levels of type I IFNs and of IFN lambda2 whereas ISG15 was far more elevated in adults. Moreover, levels of all type I IFNs, and of IFN lambda2, were significantly higher in individuals with no symptoms (65% of children and 44% of the young adults), whereas ISG15 was elevated in those with a mild COVID-19.
**Conclusion:** The higher baseline expression of IFN-related genes in children may prompt a quicker activation of the IFN response after SARS-CoV-2 infection and contribute to effective control of viral replication; the higher ISG activation in adults may be caused by the inflammatory response and associated to COVID-19 symptoms.

## 312 DIFFERENTIALLY EXPRESSED IMMUNOLOGICAL GENES IN MILD AND SEVERE CASES OF COVID-19

New Investigator Scholar

**Gabriel Gonzalez**[1], Michael J. Carr[1], Alejandro A. Garcia[1], Rachel MacCann[2], John S. Lambert[3], Eoghan De Barra[4], Eoin Feeney[2], Obada Yousif[5], Peter Doran[1], Alan Landay[6], Aoife G. Cotter[1], William W. Hall[1], Patrick Mallon[1]
*[1]University College Dublin, Dublin, Ireland, [2]Saint Vincent's University Hospital, Dublin, Ireland, [3]Mater Misericordiae University Hospital, Dublin, Ireland, [4]Beaumont Hospital, Dublin, Ireland, [5]Health Services Executive, Dublin, Ireland, [6]Rush University, Chicago, IL, USA*

**Background:** Coronavirus disease 2019 (COVID19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has varied clinical presentations from mild subclinical to severe disease with high mortality. Our aim was to determine whether examining immune-related gene expression early in infection could predict progression to severe disease.
**Methods:** In subjects of the All Ireland Infectious Diseases Cohort study, we analysed expression of 579 genes with the NanoString nCounter Immunology panel in peripheral blood mononuclear cells in those with confirmed SARS-CoV-2 infection collected within 5 days of symptom onset and matched SARS-CoV-2 negative controls with respiratory infection. Subsequent maximum COVID19 disease severity was classified as mild or severe. Read counts were normalized using panel housekeeping genes. Expression changes in severity groups were estimated against control baseline.
**Results:** Between April and July of 2020, we recruited 120 subjects, 62 with COVID19 and 58 controls, with average age 59 y.o. (IQR 34-88), 66% males and 69% Caucasian ethnicity. Maximal disease severity was used to separate COVID19 cases into mild (n=31) and severe (n=31). We identified 20 significantly deregulated genes between those with COVID19 and controls (|log2 fold|>0.5, p<0.05, Benjamin-Yekutieli p-adjustment). Function of 12 of these genes related to cytokine signaling, 9 upregulated genes to type I interferon signaling (MX1, IRF7, IFITM1, IFI35, STAT2, IRF4, PML, BST2, STAT1), while 7 downregulated genes mapped to innate immune function (IRF7, ICAM2, SERPING1, IFI16, BST2, FCER1A, PTK2). Expression in the severe group showed downregulation of FCER1A (innate immunity regulation), IL1B and TNF (inflammatory cytokines), and PTGS2 (inflammatory mediator) and greater upregulation of TNFSF4 (cytokine signaling) and PTK2 (innate immunity). Mild cases presented higher upregulation of IFIT2 (type I interferon signaling).
**Conclusion:** Observed early downregulation of regulators and mediators of inflammation in those who developed severe COVID19, suggested dysregulation of inflammation. Specifically, IFIT2 upregulation in mild cases and FCER1A downregulation in severe cases, points to early differences in host responses centered on deregulation of the interferon and inflammation responses. Whether these patterns reflect delayed interferon involvement in pathways to control the infection and contribute to pathological inflammation and cytokine storms observed in severe COVID19 requires further research.

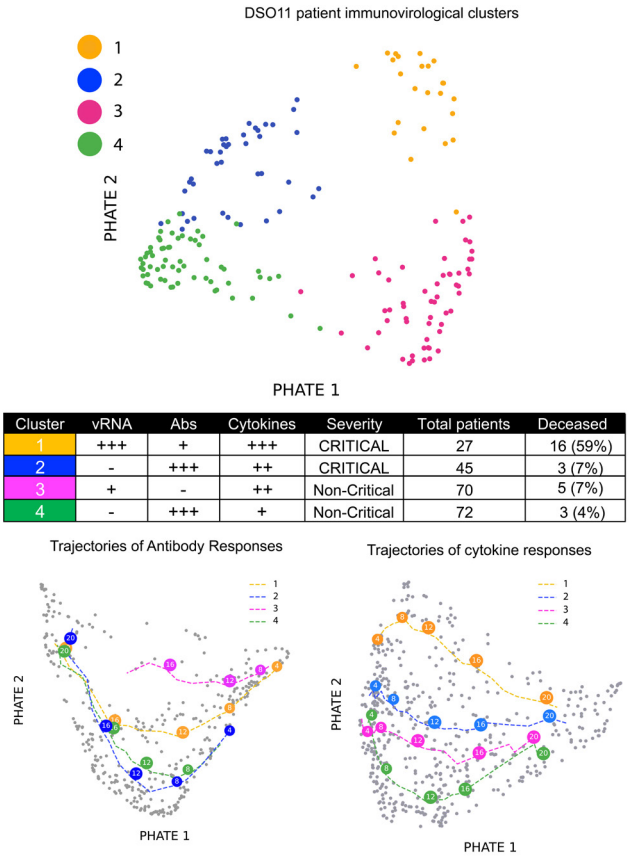



**A. Comparison of immunological expression changes in severe and mild COVID19 cases.** The horizontal and vertical axes show the logarithmic fold change against negative samples in severe and mild cases, respectively. The identity line has been added as guide for genes with similar changes. Genes have been coloured according to the significance of expression change in both (blue), only in the mild group (orange) and only in the severe group (red). **B. Comparisons of confidence intervals of $\log_2$ fold changes in between severe and mild COVID19 cases.** The vertical axes of panels show the confidence interval for the fold-change and the horizontal axes show the groups. Displayed transcripts are FCER1A, IL1B, TNF, PTGS2, IFIT2, TNFSF4 and PTK2.

## 313 DIMENSIONALITY REDUCTION FOR STEPWISE ANALYSIS OF IMMUNE RESPONSE DYNAMICS IN COVID19

**Elsa Brunet-Ratnasingham**[1], Sacha Morin[2], Marjorie Labrecque[1], Lorie Marchitto[1], Amélie Pagliuzza[1], Nathalie Brassard[1], David R. Morrisson[3], Brent Richards[4], Madeleine Durand[1], Nicolas Chomont[1], Andrés Finzi[1], Matrine Tétreault[1], Guy Wolf[2], Daniel E. Kaufmann[1]
*[1]Centre de Recherche du CHUM, Montreal, Canada, [2]Université de Montréal, Québec, Canada, [3]Lady Davis Institute for Medical Research, Montreal, Canada, [4]McGill University, Montreal, Canada*

**Background:** COVID-19 is highly heterogeneous in clinical severity and outcome. Considerable advances have uncovered biomolecular traits associated with fatal outcome. However, novel analytical tools are needed to rapidly and accurately delineate patient subgroups with various immunovirological profiles, analyze diverging disease trajectories and prioritize in-depth molecular studies.
**Methods:** To find how immunovirological features are interrelated, we profiled 12 plasma analytes (SARS-CoV-2 vRNA, SARS-CoV-2-specifc antibodies, cytokine and tissue injury markers) in 500 acute longitudinal plasma samples collected from 214 hospitalized COVID-19 patients. We analyzed them simultaneously using PHATE algorithm (potential of heat diffusion for affinity-based transition embedding, Moon et al, Nature Biotech 2019), which can reduce multiple input variables to two salient features for visualization. We performed whole blood transcriptomic analyses to identify molecular signatures associated with survival vs death in a patient cluster identified as being at extreme mortality risk.
**Results:** PHATE analysis of samples collected 11 days after symptom onset (DS011) revealed four distinct k-means clusters of patients, which aligned with disease severity and outcome. Two groups were highly enriched in critical patients requiring mechanical ventilation: a high-fatality critical cluster 1 accounted for 59% of fatal outcomes (16/27) by DS060, while critical cluster 2 had good prognosis. Clusters 3 and 4 consisted almost entirely of non-critical survivors delineated respectively by low and high antibody responses. Averaged trajectories between DS03 to DS030 diverged between clusters. All patients of the high-fatality cluster had detectable plasma vRNA, which lingered unlike the critical survivor cluster. Their antibody response had a 4-day delay, while their cytokine profile diverged from the other clusters by DS08, remaining distinct until DS022. Transcriptome profiles differed between deceased and survivors of the high-fatality cluster 1, with differential expression of GO terms associated with metabolic processes, protein regulation, cell signaling and immune pathways.
**Conclusion:** This unbiased approach gives an integrated view of dysregulated immune response components in fatal COVID-19, which may be explained through differences in molecular pathways. This approach allows to efficiently target detailed investigations on very high-risk patient subgroups who may most likely benefit from new therapeutic interventions.




| Cluster | vRNA | Abs | Cytokines | Severity | Total patients | Deceased |
|---|---|---|---|---|---|---|
| 1 | +++ | + | +++ | CRITICAL | 27 | 16 (59%) |
| 2 | - | +++ | ++ | CRITICAL | 45 | 3 (7%) |
| 3 | + | - | ++ | Non-Critical | 70 | 5 (7%) |
| 4 | - | +++ | + | Non-Critical | 72 | 3 (4%) |

**Summary Figure. Early immunovirological plasma profiles delineates diverging trajectories in SARS-CoV-2 antibody responses and cytokine production.**
**A.** PHATE visualization of cross-sectional analysis of plasma collected around 11 days after symtpom onset, merging quantities of plasma viral RNA, 8 cytokines and 3 measures of antibody response. K-means clustering atop of PHATE embedding. **B.** Summary of features per clusters, with total patient count per cluster. **C-D**. PHATE trajectory analyses : average trajectory per cluster aposed atop PHATE embedding with DSO and C) three antibody measurements or D) 8 cytokines only. Number is circle = days since symptom onset of coordinate.

## 314 T-CELL RESPONSE QUALITY TO ACUTE SARS-CoV-2 INFECTION, IMMUNE MEMORY, AND HCoV

New Investigator Scholar

**Alberto L. Perez-Gomez**[1], Carmen Gasca-Capote[1], Joana Vitalle Andrade[1], Francisco José Ostos[1], María Trujillo Rodríguez[1], Cristina Roca-Oporto[2], Nuria Espinosa-Aguilera[2], Alicia Gutiérrez Valencia[1], Mohammed Rafii-El-Idrissi Benhnia[1], Daniela Weiskopf[3], Shane Crotty[3], Alessandro Sette[3], Luis Fernando López Cortés[1], Eva Poveda[4], Ezequiel Ruiz-Mateos[1]
*[1]Institute of Biomedicine of Seville, Sevilla, Spain, [2]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [3]Center for Infectious Disease and Vaccine Research, La Jolla Institute for Immunology, La Jolla, CA, USA, [4]Galicia Sur Health Research Institute, Vigo, Spain*

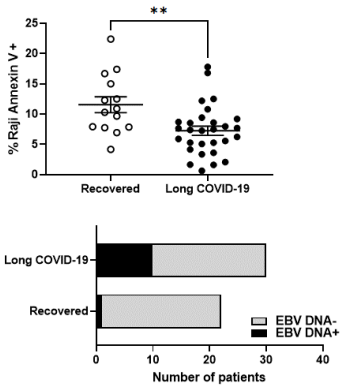
**Background:** SARS-CoV-2 specific T-cell response has been associated with disease severity, immune memory and heterologous response to endemic coronaviruses (HCoV). However, an integrative approach combining a comprehensive analysis of the quality of SARS-CoV-2 specific T-cell response and antibody levels is needed.
**Methods:** We assayed SARS-CoV-2 specific T-cell response in 103 participants. Thirty-seven (18 mild and 19 severe) were hospitalized during acute COVID-19 and 33 were recruited seven months after SARS-CoV-2 infection (19 previously hospitalized (H) and 14 non-hospitalized (NH) during acute infection). Pre-COVID-19 healthy donors (HD, n=33) were included. PBMCs were stimulated with Spike (S) and Nucleocapside (N) SARS-CoV-2 peptide pools. Likewise, an optimized peptide pool of HCoV S protein was used in HD. T-cell polyfunctionality by intracellular cytokine staining (IFN-γ, IL-2, TNF-α, CD107a and perforin (PRF)) was assayed by multiparametric flow cytometry together with measurements of T cell subsets, activation, exhaustion and senescence. Anti-S SARS-CoV-2 and HCoV IgG titers and pro-inflammatory markers were measured in plasma. Non-parametric statistic was used for the analysis.
**Results:** Mild disease was associated with high T-cell polyfunctionality biased to IL-2 production and inversely correlated with anti-S IgG levels (eg, N-specific EM CD4+ IL-2+ T-cell, r=-0.594, p=0.004). However, only IFN-γ combinations without PRF production was mostly observed for severe disease (eg, S-specific TEMRA CD4+ CD107a-IFN-γ+IL-2-PRF-TNF-α- T-cells, p=0.008). Moreover, this response was long-lasting seven months after SARS-CoV-2 infection. Both NH and H individuals presented robust anti-S IgG levels and SARS-CoV-2 specific T-cell response. In addition, only H individuals showed a T-cell exhaustion profile (eg, TEMRA CD4+ TIGIT+ T cells, p=0.0004). Combinations including IL-2, but not IFN-γ, in response to HCoV S protein, were associated with SARS-CoV-2 S-specific T-cell response in HD (eg, S-specific CM CD8+ CD107a-IFN-γ-IL-2+PRF-TNF-α- T-cells, r=5414, p=0.001).
**Conclusion:** T-cell polyfunctionality features were associated with disease severity. Moreover, T-cell response was robust seven months after infection, although previously hospitalized patients showed signs of exhaustion. SARS-CoV-2 and HCoV immune cross-reactivity have implications for protective immunity against SARS-CoV-2 to design new prototypes of vaccines in order to achieve of broader long-lasting protection against COVID-19.

## 315 IMPAIRED CYTOTOXIC IMMUNE RESPONSE AND EBV REACTIVATION IN PATIENTS WITH LONG COVID19

New Investigator Scholar

**Lorena Vigón**[1], Miguel Galán[1], Elena Mateos[1], Javier García-Pérez[1], Montserrat Torres[1], Sara Rodríguez-Mora[1], María Aranzazu Murciano-Antón[2], José Alcamí[1], Mayte Pérez-Olmeda[1], María Rosa López-Huertas[1], Mayte Coiras[1]
*[1]Institute of Health Carlos III, Madrid, Spain, [2]Centro de Salud Pedro Lain Entralgo, Alcorcón, Madrid, Spain*

**Background:** About 10% of individuals with mild infection with SARS-CoV-2 suffer from Long COVID-19, defined as signs and symptoms developed during or following COVID-19 that continue for more than twelve weeks and cannot be explained by an alternative diagnosis. In this study, we analyzed the ADCC response and the reactivation of CMV and EBV in Long COVID-19 syndrome, in comparison with patients who completely recovered from mild COVID-19
**Methods:** 30 patients with Long COVID-19 (Long COVID-19) and 20 individuals who suffered mild COVID-19 and were completely recovered (Recovered) were recruited for this study. Specific anti-SARS-CoV-2 IgG titers were analyzed by direct ELISA and their neutralizing capability was measured by using pseudovirus neutralization assay. Phenotype of CD4+ and CD8+ T cells, NK, NKT, and B cells in peripheral blood was analyzed by flow cytometry. ADCC activity was analyzed using rituximab-coated Raji cells as target. EBV and CMV reactivation in plasma was analyzed by qPCR.
**Results:** 1) 86.6% and 55.50% participants were female in Long COVID-19 and Recovered cohorts, respectively. Median age at COVID-19 diagnosis was 42y(IQR 37-46) and 45y (IQR 28-57), respectively. 2) Similar levels of CD4+ T cells were observed in both groups. However, Tregs were increased 2.8-fold in Long COVID-19 participants (p=0.0007). 3) CD8+ T cells, CD8+TCRγδ and CD8+TCRγδ were increased 1.3- (p=0.0005), 2.0- (p=0.049), and 2.5- fold (p=0.005) in Long COVID-19 individuals. 4) Expression of CD56 in NK cells and CD3-CD56+CD16+ cells were increased 1.7- (p=0.0005) and 1.7-fold (p=0.032) in Long COVID-19, respectively. 5) Specific anti-SARS-CoV-2 IgG titers were increased 2.3-fold in Long COVID-19 individuals (p=0.02) and their neutralizing capacity was increased 4.2-fold (p=0.034) in this cohort. However, ADCC activity was decreased 1.4-fold (p=0.0044). 6) Resting memory B cells were increased 2.3-fold during Long COVID-19, whereas plasmablasts were reduced 3.1-fold. 7) EBV was reactivated in 33.3% of Long COVID-19 individuals (p<0.0001), whereas CMV was not reactivated in any individual.
**Conclusion:** Despite high levels of neutralizing antibodies and cytotoxic immune populations, an impaired antibody-dependent cytotoxic activity was observed in PBMCs from individuals with Long COVID-19. This defective cytotoxic immune response may impede viral clearance, which may also contribute to EBV reactivation observed in these individuals, thereby influencing on the persistent COVID-19 symptoms.




## 316 SARS-CoV-2–SPECIFIC T CELLS ASSOCIATED WITH LUNG DYSFUNCTION IN LONG COVID-19

**Katherine M. Littlefield**[1], Renée Watson[1], Jennifer Schneider[1], Charles Neff[1], Eiko Yamada[1], Min Zheng[1], Thomas Campbell[1], Sarah Jolley[1], Andrew Fontenot[1], Brent Palmer[1]

*[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** After infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a significant number of individuals develop post-acute sequelae of COVID-19 (PASC) marked by prolonged symptoms, including persistent pulmonary dysfunction. An estimated 5-20% of those infected with SARS-CoV-2 will go on to develop PASC. T cells and inflammation contribute significantly to severe COVID-19 and similar chronic conditions; however, little is known about the role of persistent inflammation and SARS-CoV-2-specific immunity in PASC. The objective of this study is to compare inflammatory markers, frequencies of SARS-CoV-2-specific T cells, and pulmonary function in subjects who recovered from acute COVID infection (AC) and PASC.

**Methods:** We collected blood samples from 35 individuals after recovery from SARS-CoV-2 infection and divided the cohort by symptom duration into AC or PASC. We measured T cell responses to SARS-CoV-2 surface proteins, assessed levels of inflammatory markers in the plasma and measured pulmonary function. The Mann-Whitney U test were utilized to examine differences between groups. Correlations were calculated using the nonparametric Spearman test. P values of $<0.05$ were considered statistically significant.

**Results:** Compared to AC, subjects with PASC had significantly elevated plasma CRP and IL-6 and up to a hundred-fold increase in the frequency of IFN-γ- and TNF-α-producing SARS-CoV-2-specific CD4+ and CD8+ T cells in blood. Importantly, the frequency of SARS-CoV-2-specific, TNF-α-producing CD4+ and CD8+ T cells in PASC positively correlated with plasma IL-6 and negatively correlated with measures of lung function, including FEV1, while increased frequencies of IFN-γ-producing T cells were associated with the duration of respiratory symptoms during the post-acute period.

**Conclusion:** Significant immunological differences exist between subjects with PASC and AC that are associated with increased inflammation and pulmonary dysfunction, suggesting that persistent immunologic differences may drive ongoing symptoms in PASC. The persistence of SARS-CoV-2-specific T cells in PASC suggests the presence of persistent viral reservoirs as a possible mechanism behind PASC etiology.

## 317 TCR SEQUENCING OF EPITOPE-SPECIFIC T CELLS FROM SARS-CoV-2 CONVALESCENT INDIVIDUALS

**Kristin L. Boswell**[1], Phillip A. Swanson[1], Amy Ransier[1], Jesmine Roberts-Torres[1], David R. Ambrozak[1], Giune Padilla[1], Sam Darko[1], Lauren Bowman[1], Christian Wake[1], Allison Kirk[2], Paul G. Thomas[2], Adrian McDermott[1], Martin R. Gaudinski[1], Daniel C. Douek[1], Richard A. Koup[1]

*[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [2]St Jude Children's Research Hospital, Memphis, TN, USA*

**Background:** T cells have been shown to play a role in the immune response to SARS-CoV-2. Identification of T cell epitopes and a better understanding of the T cell repertoire will provide important insights into how T cells impact antiviral immunity. Here, we identified T cell epitopes within the Spike (S), Nucleocapsid (N) and Membrane (M) proteins from SARS-CoV-2 convalescent individuals and performed TCR sequencing on epitope-specific T cells.

**Methods:** Epitope mapping was performed by IFNγ ELISpot on PBMC from SARS-CoV-2 convalescent patients with mild/moderate disease (n = 19 for S; n=15 for N and M), and minimum epitopes were determined using truncated peptides and ICS. TCR sequence analysis was performed on a subset of individuals (n=9 donors; 2-3 epitopes/donor), with longitudinal samples for 7 donors (2-3 time points/donor; 33 to 236 days post-symptom onset). T cells were stimulated with individual peptides for 6 hours and sorted based on the expression of activation markers (CD4+: CD69, CD40L; CD8+: CD69, CD107a, surface TNF). scRNAseq was performed on sorted cells for TCR repertoire and transcriptome analysis.

**Results:** We identified several peptides recognized by multiple individuals, including S42 (amino acids 165-179; 7/19 donors), S302 (a.a. 1205-1219; 6/19 donors), N27 (a.a. 106-120; 6/14 donors) and M45 (a.a. 177-191; 10/14 donors). S42 elicited both CD4+ (n=5) and CD8+ (n=1) T cell responses, with one individual having both a CD4+ and CD8+ response. The minimum epitope for S42 was determined to be a 9mer (FEYVSQPFL) for both CD4+ and CD8+ cells. TCR sequencing of S42-specific T cells identified a dominant gene pairing for TCRα across multiple donors (TRAV35; TRAJ42) and for both CD4+ and CD8+ T cells (Figure 1). In general, epitope-specific CD4+ responses (S42, M45) were more clonally diverse than CD8+ responses (S42, S302, N27). For both CD4+ and CD8+ T cells, conserved TCR gene usage and gene pairings could be identified within multiple donors responding to the same epitope.

**Conclusion:** These data suggest that in SARS-CoV-2 convalescent people, epitope-specific CD4+ and CD8+ T cells can differ in their clonal diversity and that related TCRs can be identified across multiple donors. S42-specific T cell studies are ongoing to determine their transcriptional profile and pMHC presentation. Ongoing longitudinal analysis will provide a better understanding of different epitope-specific TCR repertoires and T cell transcriptional profiles, and how they evolve after infection.

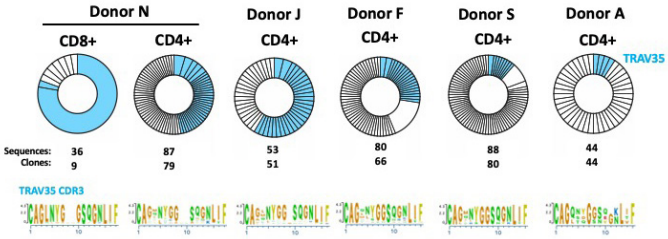



**Figure 1. S42-specific CD4+ and CD8+ T cells.** Pie charts represent the total number of sequences analyzed with each slice representing a unique clone (paired TCRα and TCRβ sequences). TRAV35-expressing clones are highlighted in blue with sequence logos of the CDR3 regions shown underneath.

## 318 CROSS-RECOGNITION OF A CONSERVED CD4+ T-CELL EPITOPE PRESENT IN DIVERSE CORONAVIRUSES

New Investigator Scholar

**Bezawit A. Woldemeskel**[1], Arbor G. Dykema[1], Caroline C. Garliss[1], Saphira Cherfils[2], Kellie N. Smith[1], Joel Blankson[1]

*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Hunter College, New York, NY, USA*

**Background:** Recent studies have shown that vaccinated individuals harbor cross-reactive T cell responses that can cross-recognize SARS-CoV-2 and endemic human common cold coronaviruses (HCoVs). However, it is still unknown whether CD4+ T cells from vaccinated individuals recognize peptides from bat coronaviruses that may have the potential of causing future pandemics. In this study, we identified a SARS-CoV-2 spike protein epitope (S815-827) that is conserved in coronaviruses from different genera and subgenera including SARS-CoV, MERS-CoV, multiple bat coronaviruses and a feline coronavirus. We hypothesized that S815-827 is recognized by vaccinated individuals, and that S815-827-reactive T cells can cross-recognize homologues bat coronaviruses.

**Methods:** To evaluate CD4+ T cell responses, we isolated CD8 depleted PBMCs from COVID-19 vaccinated individuals and performed IFN-γ ELISPOT assays. To assess T cell cross-reactivity, S815-827-reactive T cell lines were re-stimulated with homologous coronavirus peptides and cytokine production was assessed with flow cytometry. Additionally, the Vira-FEST assay (which utilizes TCR Vβ CDR3 sequencing) was performed to identify cross-reactive CD4+ T cell clones. Statistical comparisons were done using Mann-Whitney test, Wilcoxon matched-pairs signed rank test or Friedman test with Dunn's multiple comparison as appropriate.

**Results:** Our results show that 16 out of 38 (42%) of vaccinated participants in our study who received the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) COVID-19 vaccines had robust CD4+ T cell responses to S815-827. All responders also recognized homologous peptides from at least 2 other coronaviruses, and 8 out of 11 responders recognized peptides from at least 6 out of the 9 other coronaviruses tested. To determine T cell cross-reactivity, we re-stimulated S815-827 specific T cell lines with homologous coronavirus peptides. We found that S815-827 specific T cells had a robust increase in IFN-γ+ TNF-α+ expression upon re-stimulation with other peptides. We next used the Vira-FEST assay to confirm cross-reactivity by assessing if the same CD4+ T receptor clonotypes recognize both S815-827 and homologous bat coronavirus peptides. In all 3 participants tested, we identified multiple cross-reactive T cell receptors that recognize both S815-827 and homologous bat coronavirus peptides.
**Conclusion:** Our results suggest that current mRNA vaccines elicit T cell responses that can cross-recognize bat coronaviruses, and thus might induce protection.

## 319 DEFINING IMMUNOGENIC PEPTIDES TARGETING SARS-CoV-2 VARIANTS OF CONCERN

New Investigator Scholar

**Eunok Lee**[1], Gabriel Duette[1], Gabriela Martins Costa Gomes[1], Katie Tungatt[1], Chloe Doyle[1], Ashley Lee[1], Vicki Stylianou[1], Rajiv Khanna[2], Kerrie Sandgren[1], Anthony Cunningham[1], Sarah Palmer[1]
*[1]The Westmead Institute for Medical Research, Westmead, Australia, [2]QIMR Berghofer Medical Research Institute, Brisbane, Australia*

**Background:** Identifying Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) specific T-cell epitope-derived peptides that are also found within variants of concern (VOC) is critical for measuring the duration of cellular immunity induced by the virus and COVID-19 vaccines. Therefore, we assessed whether the peptides selected from topologically important regions of SARS-CoV-2 proteins avoid major mutations of VOC and induce T-cell immune response.
**Methods:** We selected 32 peptides within topologically important regions of SARS-CoV-2 Spike (S) and Nucleocapsid (NC) proteins by applying an insilico pipeline to 607 viral sequences in 2019. To determine if these peptides avoid VOC mutations, we analyzed S and NC protein regions derived from 1.7 x 10^6 viral genomic sequences compiled from Mar 2020-Aug 2021. We identified α-, β- and δ-VOC mutations found within >1% of the S and NC protein sequences. These mutations were compared to the peptides. To determine T-cell immune response to these selected peptides as a pool, we assessed interferon-γ (IFN-γ), interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α) and CD107a/b (degranulation marker) production within peripheral blood mononuclear cell (PBMC) samples derived from COVID-19 post-recovery donors (n=23) by employing dual color FluoroSpot and intracellular cytokine staining (ICS).
**Results:** We found 88% of S protein-derived peptides did not contain mutations of α-, β- and δ-VOC. All peptides from S protein (n=25) avoided known T-cell escape mutations. Of the 7 NC-derived peptides, three contained the L139F mutation found within α- and δ-VOC, however, this mutation was observed within <2% NC protein sequences. A peptide pool containing our 32 selected peptides elicited an immune response within PBMCs from 17/23 COVID-19 post-recovery donors. FluoroSpot analysis revealed IFN-γ and IL-2 production to our peptide pool was similar/higher compared to the commercial S and NC peptide pools. The response of CD4 and CD8 T-cells to our peptide pool was polyfunctional expressing ≥2 markers within most of the donors when ICS was performed, with IFN-γ and TNF-α being the main cytokines produced.
**Conclusion:** Applying an immunoinformatics pipeline allowed us to select peptides from the S and NC proteins which avoid the majority of mutations found within the α-, β- and δ-VOC. Our peptide pool elicited a polyfunctional T-cell response making it an ideal candidate for assessing the duration of cellular immunity induced by SARS-CoV-2 variants and vaccines.

## 320 PREDICTING COVID-19 CLINICAL PROTECTIVE IMMUNITY FROM SARS-CoV-2 T-CELL RESPONSES

**Amanda M. Buck**[1], Darra Drucker[1], Michael J. Peluso[1], Steven G. Deeks[1], Rachel L. Rutishauser[1], Timothy J. Henrich[1], Amelia N. Deitchman[1]
*[1]University of California San Francisco, San Francisco, CA, USA*

**Background:** SARS-CoV-2 produces variable immune responses leading to different levels of immune protection. The relationship between neutralizing antibody level (NAb) and protective immunity has been well characterized after infection and vaccination. While comparatively specific T cell responses tend to be more variable, the impacts of these responses have broad implications on long-term immunity and their role in protective immunity has not been as clearly defined. Using data from our prospective cohort study and studies of clinical protective immunity/efficacy (from vaccines), we predicted protective immunity over time in relation to SARS-CoV-2-specific T cell dynamics.
**Methods:** With linear mixed-effects models from our published immune data from people recovering from COVID-19, we simulated the Spike (S)-specific interferon-γ (IFNγ)+ CD4+, S-specific IFNγ+ CD8+, and nucleocapsid (N)-specific IFNγ+ CD8+ T cells over time (n=500 individuals). We then predicted NAbs from linear regression models developed from the same cohort. Finally, protective immunity from NAb titers was simulated from a published model. We similarly simulated 25, 50, and 75% lower T cell responses than those observed post-COVID-19 to understand how immune response variation may impact protective immunity.
**Results:** Virus-specific T cell responses resulted in similar protective immunity across T cell subsets, but with differences in variability over time. Protective immunity for IFNγ+ S CD8 T cells spanned from 86-95%, while for IFNγ+ S CD4 T cells and IFNγ+ N CD4 T cells it ranged from 81-96% and 84-95% respectively. Further, based on simulated dampened T cell responses, protective immunity overall did not drop below 81% less than nine months after infection even with a 75% reduction in specific T cell immunity.
**Conclusion:** NAbs are often the singular focus to predict protective immunity and the role of virus-specific T cell immunity has often been discussed as a secondary immune response. Our analysis demonstrates that for SARS-CoV-2, certain T cells responses can reliably predict protective immunity and may be intrinsically linked. Simulating dampened T cell response to mimic a more virulent strain or inadequate immune response, demonstrated that dampened T cell response may not be responsible for inadequate protective immunity in these scenarios. In the absence of prospective clinical data, similar models may be utilized to explore the impact of potential therapeutics on immune responses and resulting protective immunity.

## 321 NATURAL KILLER CELL-MEDIATED ADCC IN SARS-CoV-2 INFECTION AND VACCINATION

New Investigator Scholar

**Kerri Hagemann**[1], Johannes Jung[1], Heike Hildebrandt[1], Stephan Menzel[2], Madeleine Bunders[1], Friedrich Koch-Nolte[2], Fabian Heinrich[2], Sven Peine[2], Julian Schulze Zur Wiesch[2], Thomas T. Brehm[2], Marylyn M. Addo[2], Marc Lütgehetmann[2], Marcus Altfeld[1]
*[1]Heinrich Pette Institute, Hamburg, Germany, [2]University Medical Center Hamburg–Eppendorf, Hamburg, Germany*

**Background:** COVID-19, caused by SARS-CoV-2, has emerged as a global pandemic. While immune responses of the adaptive immune system have been in the focus of research, the role of Natural killer (NK) cells in COVID-19 remains poorly understood.
**Methods:** We characterized NK cell-mediated SARS-CoV-2 antibody-dependent cellular cytotoxicity (ADCC) against SARS-CoV-2 spike-1 (S1) and nucleocapsid (NC) protein using NK cell degranulation (CD107a) and killing assays.
**Results:** Serum samples from SARS-CoV-2 resolvers induced significant CD107a expression by NK cells in response to S1 and NC ($p < 0.0001$), while serum samples from SARS-CoV-2-negative individuals did not. Furthermore, serum samples from individuals that received the BNT162b2 vaccine induced strong CD107a expression by NK cells that increased with the second vaccination and was significantly higher than observed in infected individuals ($p < 0.0001$). As expected, vaccine-induced responses were directed against S1 and not against NC protein. S1-specific CD107a responses by NK cells were significantly correlated to NK cell-mediated killing of S1-expressing cells ($r = 0.86$, $p = 1.82 \times 10^{-6}$). Interestingly, screening of serum samples collected prior to the COVID-19 pandemic identified two individuals with cross-reactive antibodies against SARS-CoV-2 S1, which also induced degranulation of NK cells.
**Conclusion:** These data demonstrate that antibodies induced by SARS-CoV-2 infection and anti-SARS-CoV-2 vaccines can trigger significant NK cell-mediated ADCC activity, and identify some cross-reactive ADCC activity against SARS-CoV-2 by endemic coronavirus-specific antibodies.

## 322 DIVERGENT ADAPTIVE IMMUNE RESPONSES DEFINE 2 TYPES OF LONG COVID

**Kervevan Jérôme**[1], Isabelle Staropoli[1], Dorsaf SLAMA[2], Raphaël Jeger-Madiot[1], Delphine Planas[1], Marie-Pierre Pietri[2], Rémy Robinot[1], Faroudy Boufassa[3], Olivier Schwartz[1], Dominique Salmon[2], Lisa A. Chakrabarti[1]
*[1]Institut Pasteur, Paris, France, [2]Hôtel Dieu Hospital, AP-HP, Paris, France, [3]INSERM U1018, Le Kremlin-Bicêtre, France*

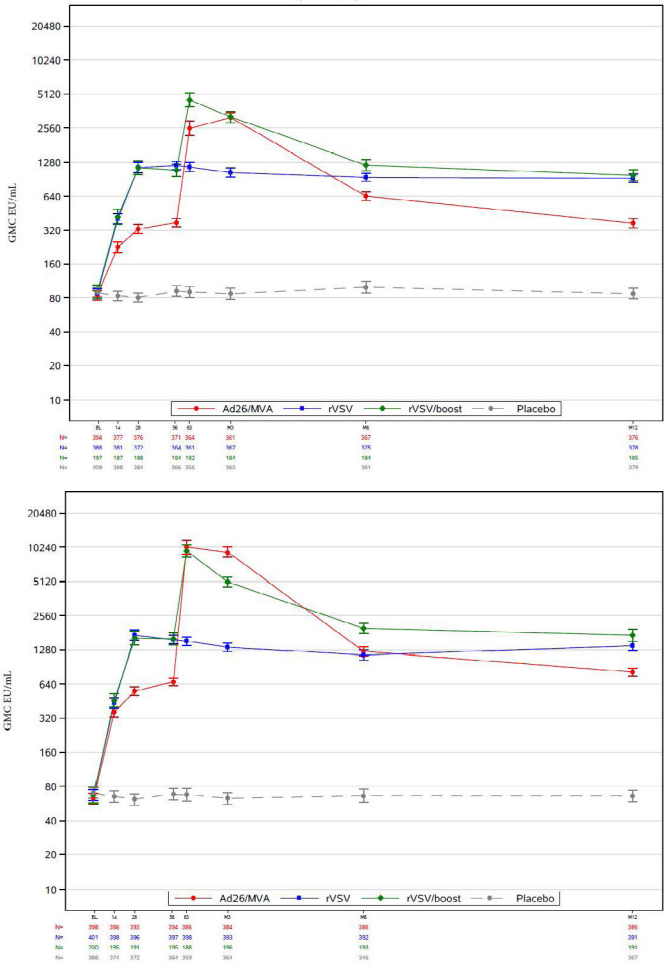
**Background:** More than 10% of patients infected with SARS-CoV-2 experience a Long COVID syndrome, characterized by the persistence of a diverse array of symptoms where fatigue predominates. The role of the adaptive immune response in Long COVID remains poorly understood, with contrasting hypotheses suggesting either an insufficient antiviral response or an excessive immune response that would trigger autoimmune damage. To address this issue, we set to characterize humoral and cellular responses in Long COVID patients prior to SARS-CoV-2 vaccination.
**Methods:** Long COVID patients (n=36) were included based on (1) an initial SARS-CoV-2 infection documented by PCR or the conjunction of two major signs of COVID-19 and (2) the persistence or resurgence of symptoms for over 3 months. They were compared to convalescent COVID patients with resolved symptoms (n=23) and uninfected control individuals (n=20). IgG and IgA antibodies specific to the SARS-CoV-2 spike were detected by a sensitive S-flow assay, which measures antibody binding to spike-expressing 293T cells. For CD4+ T cell response analyses, cytokine production was measured by intracellular staining on primary T cell lines stimulated by immunodominant peptides derived from the S, M, and N viral proteins.
**Results:** Antibody analyses revealed either strong or very low/undetectable amounts of spike-specific IgG in sera from Long COVID patients, thus distinguishing a seropositive and a seronegative group. Seropositive Long COVID patients (n=21) showed strong CD4 responses that tended to be of higher magnitude than those of convalescents ($P<0.05$ for 2 immunodominant peptides). In contrast, seronegative Long COVID patients (n=15) showed low or undetectable CD4+ T cells responses, with 4/15 patients showing responses above those observed in healthy donors. CD4+ T cell responses correlated with spike-specific IgG responses in seropositive Long COVID patients ($P\leq0.002$) but not in convalescents, pointing to differences in immune memory persistence.
**Conclusion:** These findings highlight divergent adaptive immune responses among Long COVID patients, with a group characterized by seroconversion and particularly strong CD4+ T cell responses, and a second group characterized by low or undetectable antibody and cellular responses. Further studies are warranted to determine whether the etiology and the duration of symptoms differ in these two groups of Long COVID patients.

## 323 PREVAC RCT: EFFECTS OF 3 EBOLA VACCINE STRATEGIES IN WEST AFRICAN ADULTS AND CHILDREN

**Mark Kieh**[1], Laura Richert[2], Abdoul Habib Beavogui[3], Birgit Grund[4], Bailah Leigh[5], Eric D'Ortenzio[6], Seydou Doumbia[7], Samba Sow[8], Lisa Hensley[9], Yves Levy[10], Cliff Lane[9], Deborah Watson-Jones[11], James Neaton[4], Yazdan Yazdanpanah[6]
*[1]Partnership for Research on Ebola Virus in Liberia (PREVAIL), Monrovia, Liberia, [2]Institut National de la Santé et de la Recherche Médicale, Bordeaux, France, [3]Centre National de Formation et de Recherche en Santé Rurale de Maferinyah, Maferinyah, Guinea, [4]University of Minnesota, Minneapolis, MN, USA, [5]College of Medicine and Allied Health Sciences (COMAHS), Freetown, Sierra Leone, [6]Institut National de la Santé et de la Recherche Médicale, Paris, France, [7]University Clinical Research Center (UCRC), Bamako, Mali, [8]Center for Vaccine Development and Global Health (CVD), Bamako, Mali, [9]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [10]Institut National de la Santé et de la Recherche Médicale, Créteil, France, [11]London School of Hygiene & Tropical Medicine, London, UK*

**Background:** Questions remain concerning the safety, durability and kinetics of immune responses, particularly in children, for vaccines that have been used to prevent Ebola virus disease (EVD).
**Methods:** A randomized, double-blind, Phase II trial was conducted in West Africa to compare the safety and immunogenicity of three vaccine strategies against EVD with placebo: the Ad26.ZEBOV vaccine followed by the MVA-BN-Filo vaccine (Ad26/MVA) given at 56 days, and the rVSVΔG-ZEBOV-GP vaccine (rVSV) given without an rVSVΔG-ZEBOV-GP boost or with boost (rVSVB) at 56 days. IgG antibody concentrations were measured at baseline, at days 7, 14, 28, 56, and 63, and at months 3, 6, and 12. The primary immunogenicity endpoint was assessed at month 12; antibody responders were defined as participants with both a 4-fold increase or greater from baseline and an antibody concentration≥ 200 EU/mL.
**Results:** 1,400 adults and 1,401 children were randomized to receive Ad26/MVA, rVSV, rVSVB, or placebo. The median (25th, 75th percentiles) age of adult participants was 27 (20, 38) years; 45% were female. One-third of children were enrolled in each of the age groups 1-4, 5-11, and 12-17 years, and 46% were female. Compared to placebo, both adults and children in the vaccination groups reported more injection site reactions and symptoms, almost exclusively of low-grade severity, in the week following the prime and second (MVA) or booster (rVSV) vaccinations. These differences were not seen at subsequent follow-up visits. Serious adverse events were uncommon and did not differ significantly between the vaccine groups and the placebo group. The percentages of antibody responders among adults and children at month 12 were 41% and 79%, respectively, for Ad26/MVA, 76% and 87% for rVSV, 81% and 93% for rVSVB, and 2.7% and 3.6% for placebo ($p<0.001$ for all comparisons with placebo). Significant differences ($p<0.001$) in the percentage of antibody responders between each vaccine group and placebo were evident by day 14.
**Conclusion:** Both adults and children evidenced significant immune responses to the three Ebola vaccine strategies at month 12. Side effects were generally mild and moderate and were time-limited for each vaccine for both children and adults.

Figure: Geometric Mean Concentration by Visit: Adults (top) and Children (bottom)



## 324 EBOLA VACCINE-INDUCED STRONG-BINDING ANTIBODY RESPONSES IN PEOPLE LIVING WITH HIV-1

New Investigator Scholar

**Thembi Mdluli**[1], Suzanne Wollen-Roberts[1], Dominic Paquin-Proulx[1], Jay Hooper[2], Betty Mwesigwa[3], Josphat Kosgei[4], Janet Oyieko[4], Nyanda Ntinginya[5], Ilesh Jani[6], Michael Iroezindu[1], Lucy Ward[7], Kerstin Luhn[8], Cynthia Robinson[8], Julie Ake[1], Morgane Rolland[1]

*[1]US Military HIV Research Program, Silver Spring, MD, USA, [2]US Army Medical Research Institute of Infectious Diseases, Frederick, MD, USA, [3]Makerere University Walter Reed Project, Kampala, Uganda, [4]Kenya Medical Research Institute, Nairobi, Kenya, [5]National Institute for Medical Research, Mbeya, Tanzania, United Republic of, [6]Polana Caniço Health Research and Training Center, Maputo, Mozambique, [7]US Department of Defense, Fort Detrick, MD, USA, [8]Janssen Prevention and Vaccines, Leiden, Netherlands*

**Background:** Johnson & Johnson's Ebola vaccine was approved by the European Union for the prevention of Ebola Virus Disease in 2020. The vaccine corresponds to the adenovirus type 26 vector encoding Zaire Ebolavirus (EBOV) glycoprotein (GP) (Ad26.ZEBOV) and the modified vaccinia Ankara vector encoding GP from EBOV, Sudan virus (SUDV) and Marburg virus (MARV) and nucleoprotein from Tai Forest virus (TAFV) (MVA-BN-Filo) administered 8 weeks later. We conducted a systems immunology analysis of antibody (Ab) responses induced after different vaccination schedules in participants from the United States and Africa (Kenya, Mozambique, Nigeria, Tanzania, Uganda), including people living with HIV (PLWH).

**Methods:** Vaccine and placebo group specimens from the EBL2003/RV456 Phase II clinical trial were analyzed at baseline and peak immunogenicity following MVA-BN-Filo and Ad26.ZEBOV immunizations two weeks apart (n = 71; US (57 vaccinees) and 38 African (31 vaccinees) participants) or Ad26.ZEBOV and MVA-BN-Filo vaccination four weeks apart (n = 147 African participants, 117 vaccinees). A multiplex immunoassay was used to map Ab responses to 9 filovirus antigens (EBOV, SUDV, MARV, Reston, Bundibugyo (BDBV)) and 3 HIV antigens. Functional assays included Ab-dependent complement deposition, cellular phagocytosis, NK cell activation and neutralization against EBOV and BDBV pseudoviruses.

**Results:** Both vaccination schedules induced high Ab responses specific to EBOV GP with rare and low responses to other SUDV and Reston antigens. IgG responses did not significantly differ according to vaccination schedule (either Ad26.ZEBOV or MVA-BN-Filo immunization first) or country of origin. Antibody responses were durable, as 77% of participants still had EBOV IgG responses at least 3-fold over baseline one year post vaccination. The vaccine profile was defined through random forest by high Ab binding neutralizing and Fc effector responses towards EBOV. PLWH showed binding and neutralizing responses that were comparable to those in uninfected participants, although Fc effector functions were lower in PLWH. Variation in binding or functional responses across PLWH did not associate with their HIV viral loads.

**Conclusion:** We demonstrated that the two vaccination schedules induced responses focused on the expected vaccine target (EBOV GP) and elicited strong binding and neutralizing responses in PLWH. Importantly, responses in PLWH were comparable to those in uninfected participants across multiple countries and continents.

## 325 SINGLE-CELL IMAGING CORROBORATES THE LINK BETWEEN HIV INTEGRATION AND TRANSCRIPTION

**Julie Janssens**[1], Flore De Wit[1], Nagma Parveen[2], Frauke Christ[1], Zeger Debyser[1]

*[1]Katholieke Universiteit Leuven, Leuven, Belgium, [2]Indian Institute of Technology Kanpur, Kanpur, India*

**Background:** Antiretroviral treatment fails to cure HIV infection since latent provirus resides in long-lived cellular reservoirs, rebounding whenever therapy is discontinued. The molecular mechanisms underlying HIV latency are complex whereby the possible link between integration site selection and the transcriptional state of the provirus is poorly understood. HIV integration is targeted towards active chromatin by the direct interaction with a host protein, LEDGF/p75. Small molecules, referred to as LEDGINs, inhibit the LEDGF/p75-integrase (IN) interaction and shift integration out of active genes resulting in residual provirus that is more latent.

**Methods:** We now have used a branched DNA imaging method for simultaneous detection of viral DNA and RNA in single cells. We investigated how LEDGIN treatment affects the location, transcription and reactivation of the provirus in both cell lines and primary cells. LEDGIN CX014442 was tested and compared to equivalent concentrations of raltegravir (RAL), a clinically approved IN strand transfer inhibitor. After infection of the cells in the presence of the compounds, the cells were kept in culture to allow silencing of the viral gene expression and were reactivated on day 7 (PBMCs) or 10 (cell lines) post infection.

**Results:** LEDGINs inhibited HIV infection, as shown by a decrease in the number of vDNA spots per cell. Furthermore, the 3D nuclear location of the residual provirus after LEDGIN treatment was shifted towards the inner nucleus. LEDGIN-mediated retargeting hampered both the baseline transcriptional state and transcriptional reactivation of the provirus, as shown by a decrease in the number of vRNA spots per cell. LEDGIN treatment reduced the vRNA expression per residual copy. Since RAL failed to reduce HIV transcription and reactivation, this effect is not merely the result of reduced infectivity. Paradoxically, at a higher concentration of LEDGIN an increase in the number of vDNA spots per cell was observed in primary cells. This may reflect a positive selection of deep-latent provirus after LEDGIN treatment.

**Conclusion:** In conclusion, retargeting integration with LEDGINs shifted the 3D location, reduced transcription and hampered reactivation of the provirus. These results corroborate the crucial role of integration site selection for the transcriptional state of the provirus and support block-and-lock functional cure strategies in which the latent reservoir is permanently silenced after retargeting.

## 326 SINGLE-CELL PROFILING OF LEAKY LATENT HIV-1 RESERVOIRS IN ART-TREATED DONORS

**Mathieu Dubé**[1], Nathalie Brassard[1], Rémi Fromentin[1], Gérémy Sannier[1], Gloria G. Delgado[1], Amélie Pagliuzza[1], Jean-Pierre Routy[2], Nicolas Chomont[1], Daniel E. Kaufmann[1]

*[1]Centre de Recherche du CHUM, Montreal, Canada, [2]McGill University, Montreal, Canada*

**Background:** A major obstacle to HIV cure is the persistence of latent viral reservoirs. Even during ART, latently infected cells can maintain a certain degree of transcriptional "leakiness" characterized by a basal level of viral transcription. Cell-associated HIV RNA has been associated with a shorter time to viral rebound at ART interruption, demonstrating this phenomenon's biological relevance. However, leaky latency in vivo remains poorly understood.

**Methods:** We studied leaky latency in 15 people living with HIV with optimal viral suppression on ART (ART-PLWH). Purified CD4 T cells were either PMA/ionomycin-stimulated (inducible) or unstimulated (leaky) for 16h. Transcriptionally active (vRNA+) viral reservoirs were identified by single-cell flow cytometric fluorescent in situ RNA hybridization (RNAflow-FISH) using probes targeting LTR-gag, gag, or pol regions. Cells were further stained for p24 protein and phenotypic markers and acquired on a Symphony flow cytometer.

**Results:** We detected leaky vRNA+ cells in 80% of the participants, compared to 87% for induced vRNA+. We detected a median of 21 leaky vRNA+ / million CD4 T cells, significantly higher than the 4 /million false-positive rate in uninfected volunteers. This represented a median of 30% of the inducible vRNA+ (median 62/million) and 4% of the cells containing integrated HIV DNA (int.DNA+, median 686/million). Leaky vRNA+ cells correlated with int.DNA+ ($r=0.58$, $p=0.03$), and strongly with induced vRNA+ ($r=0.82$, $p<0.001$). Compared to induced vRNA+ cells, leaky vRNA+ showed low single-cell transcription yields and short abortive elongation (median 86% of gagRNA+polRNA- transcripts compared to 52% for inducible) incompatible with p24 translation. As demonstrated for induced vRNA+ cells, leaky vRNA+ cells were rarely in naïve-like CD45RA+CCR7+ cells (median 3.6-fold decrease compared to the parental CD4 population, $p=0.002$) and were modestly but consistently enriched in central memory CD45RA-CCR7+ cells (1.2-fold increase, $p=0.01$).

**Conclusion:** Our results demonstrate that leaky latency is detectable in most ART-PLWH and correlates strongly with inducible reservoirs. Their transcription profile is reminiscent of the reported block(s) to elongation described in the absence of stimulation. Both leaky and inducible reservoirs appear to share a preference for central memory at the expense of naïve cells. All these observations raise the possibility that leakiness is a precursor state poise for induction.

## 327 TRANSLATION-COMPETENT HIV RESERVOIRS ARE HIGHLY EXPANDED AND PHENOTYPICALLY DIVERSE

New Investigator Scholar

**Caroline Dufour**[1], Corentin Richard[1], Rémi Fromentin[1], Marion Pardons[1], Marta Massanella[1], Ben Murrell[2], Bertrand Routy[1], Jean-Pierre Routy[3], Nicolas Chomont[1]

*[1]Université de Montréal, Montreal, Canada, [2]Karolinska Institute, Stockholm, Sweden, [3]McGill University Health Centre, Montreal, Canada*

**Background:** Understanding the dynamics of viral persistence in people living with HIV (PLWH) receiving ART is a key step to develop an HIV cure. HIV persists as an integrated provirus in a small pool of latently infected cells. Of note, only a fraction of these cells produces viral products when activated. We combined HIV-Flow with a modified FLIPS assay to assess the integrity and the clonality of translation-competent and inducible proviruses compared to non-induced genomes.

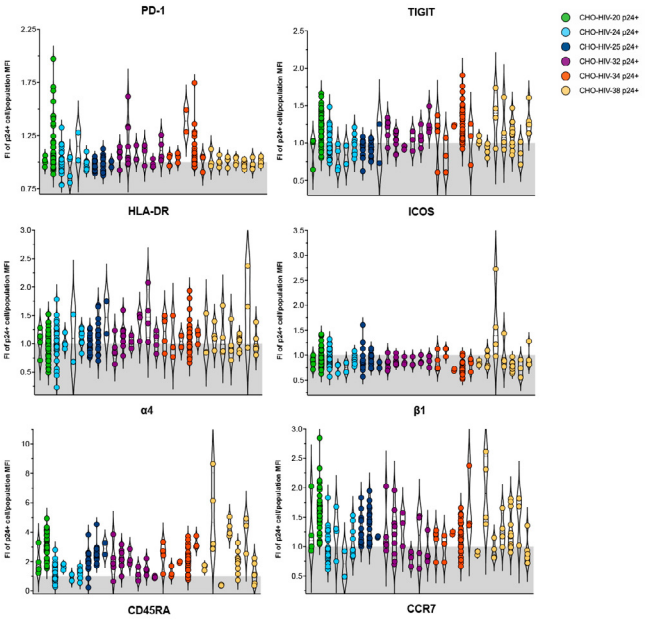
**Methods:** CD4+ T cells from 6 PLWH on ART were stimulated for 24h with PMA/ionomycin and p24+ cells were index-cell sorted using a panel of markers including CD45RA, CCR7, PD-1, TIGIT, ICOS, HLA-DR, integrins α4 and β1. p24- bulk cells containing non-induced proviruses were simultaneously sorted. Individual proviruses from single-sorted p24+ cells and serial-diluted bulk p24- cells were amplified by nested PCR and sequenced using PacBio. p24+ proviruses integrity and clonality were associated with the expression levels of each cellular marker.

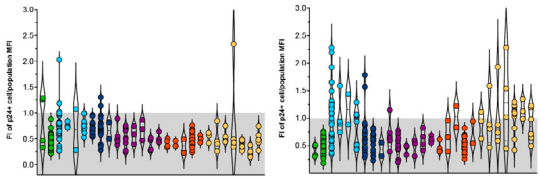
**Results:** We obtained 309 proviral sequences from single-sorted p24+ cells and 334 from p24- bulk population. Despite their ability to express viral protein, 96% of the viral genomes obtained from p24+ single-sorted cells were defective, particularly in the packaging signal (64% of all defects), while the p24- bulk population included 98% defective proviruses, mostly due to large deletions (79%). This difference in the type of defects between p24+ and p24- cells was highly significant ($p<0.0001$). Clonal expansions (cells sharing the exact same HIV genome) were more frequent in p24+ cells compared to p24- cells (79% and 52% respectively; $p<0.0001$). Importantly, identical proviruses shared between p24+ and p24- cells were observed in 5 of the 6 participants, indicating that efficient reactivation from latency is not solely driven by viral features. In p24+ cells, levels of expression of cellular markers greatly varied within a given proviral clone (Fig. 1), revealing the plasticity in the phenotype of the expanded clones.

**Conclusion:** The translation-competent and inducible HIV reservoir is highly clonal and shares clonally expanded sequences with the non-induced reservoir. Identical proviruses are found in p24+ cells displaying diverse phenotypes, indicating that clonal expansions contribute to the phenotypic diversification of HIV reservoirs.

**Fig.1: Levels of expression of 8 phenotypic markers at the surface of p24+ cells harboring 100% identical HIV proviruses.**

Each dot represents HIV proviral sequence from a single sorted p24+ cells and are color-coded for each participant. Each violin plot represents an individual clonal expansion. The grey zone indicates the FI measures that are below the MFI of the total T cell population.



## 328 LONG-READ SEQUENCING ASSAY ALLOWS ACCURATE CHARACTERIZATION OF THE HIV-1 RESERVOIR

New Investigator Scholar

**Laurens Lambrechts**[1], Rita Verstraeten[1], Noah Bonine[1], Ytse Noppe[1], Marion Pardons[1], Basiel Cole[1], Linos Vandekerckhove[1]

*[1]HIV Cure Research Center, Ghent University, Ghent, Belgium*

**Background:** The advent of near full-length (NFL) HIV-1 proviral genome sequencing greatly expanded our understanding of the quality of the viral reservoir, revealing that only 2-5% of the persistent proviruses in ART-treated individuals can be considered genome-intact. However, current NFL assays are based on labor-intensive and costly principles of repeated PCRs at limiting dilution, restricting their scalability. We developed a long-read sequencing assay to characterize many proviral genomes in parallel from bulk DNA.

**Methods:** The sensitivity of the long-read assay was determined on a DNA dilution series of J-Lat in uninfected Jurkat ranging from 80,000 to <8 HIV-1 copies. Next, the assay was performed on 15 chronic ART-suppressed individuals, using a fixed input of 500 ng DNA extracted from peripheral blood CD4 T cells (reservoir sizes ranging from 321 to 6581 total HIV-1 DNA copies/million CD4 T cells). Individual proviruses were tagged with a different unique molecular identifier (UMI) at each end during a single reaction, followed by NFL PCR amplification and long-read sequencing on an Oxford Nanopore MinION. UMI-based demultiplexing allowed for the construction of highly accurate consensus genomes, while excluding aberrant chimeric PCR artefacts. In addition, Full-Length Individual Provirus Sequencing (FLIPS) was performed on 2 individuals. Data from both assays were compared through phylogenetic analyses.

**Results:** The lower limit of the long-read assay was found to be <8 HIV-1 copies. The long-read assay yielded an average of 14 distinct HIV-1 proviruses per participant (range: 3-42). Across all participants, 213 distinct proviruses were retrieved of which 8% were considered putatively intact. In terms of reservoir composition, data obtained with FLIPS showed an overall agreement with data obtained with the long-read assay. In an individual with limited clonality (6% clonality of FLIPS data, n=1 clone) only 1 overlapping provirus was found, while an overlap of 3 proviruses was observed in an individual with higher clonality (91% clonality of FLIPS data, n=4 clones). Comparing the 4 overlapping proviral consensus genomes to their matching FLIPS counterparts showed an average sequence accuracy of 99,97%.

**Conclusion:** The long-read assay offers a high-throughput NFL sequencing method which enables an accurate characterization of the proviral landscape while retaining sequencing accuracy comparable to current gold standard NFL assays.

## 329 HIV-1 PROVIRUS-HOST CHROMATIN INTERACTIONS AT THE INTEGRATION SITE

New Investigator Scholar

**Jack A. Collora**[1], Sandra Springer[1], Yuval Kluger[1], Ya-Chi Ho[1]

*[1]Yale University, New Haven, CT, USA*

**Background:** Retroviral elements and HTLV-1 leverage the linearly proximal and 3D chromatin environment to regulate viral and host gene transcription at the integration site. We hypothesize that HIV-1 integration changes local host chromatin environment and potentiates HIV-1 insertional mutagenesis.

**Methods:** To understand HIV-1 proviral-host chromatin interactions, we examined the global chromatin architecture (using HiC), enhancer connectome (using H3K27Ac HIChIP), chromatin accessibility (using ATAC-seq), and gene expression (using strand-specific RNAseq) in 4 HIV-1-infected Jurkat T cell clones having known HIV-1 integration sites. Further, we designed HIV-1 LTR 4C-seq to examine HIV-1 LTR interaction with the host chromatin.

**Results:** Using HiC and H3K27Ac HIChIP, we found that the global host chromatin architecture was not dramatically impacted surrounding the integration site, suggesting that HIV-1 may leverage existing chromatin interactions but may not remodel the chromatin interactions globally. Using HIV-1 LTR 4C-seq, we found that HIV-1 LTR interacted with the host chromatin up to 500 kb upstream and downstream from the integration site. Using

ATACseq, we found that there was increased chromatin accessibility up to 10 kb downstream of HIV-1 integration site but not upstream. HIV-1 increased the magnitude of existing host chromatin accessibility peak immediately downstream of HIV-1 integration site. Our finding suggests that HIV-1 increases chromatin accessibility in a location and orientation-dependent manner. When we integrated HIV-1 LTR 4C-seq and ATACseq results, we found that the accessible peaks in regions that HIV-1 interacts with are enriched for STAT5 binding sites. Of note, STAT5 is known to bind to HIV-1 LTR, and HIV-1 integration into STAT5A and STAT5B is enriched in clonally expanded HIV-1-infected cells.
**Conclusion:** HIV-1 integration increases chromatin accessibility immediately downstream the integration site. HIV-1 interacts with distal host chromatin where STAT5 binds. Our results suggest a role for STAT5 in regulating HIV-1-host chromatin interactions.

## 330 SINGLE-CELL MULTIOMICS ANALYSIS OF HIV RESERVOIR CELLS BY NOVEL T-TRACE APPROACH

New Investigator Scholar

**Julie Frouard**[1], Jason Neidleman[1], Rebecca Hoh[2], Steven G. Deeks[2], Warner Greene[1], Nadia Roan[1]
*[1]Gladstone Institute of Virology and Immunology, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA*

**Background:** We recently reported PP-SLIDE as a method taking advantage of high-dimensional phenotyping by CyTOF to phenotype and enrich for inducible reservoir cells from virally-suppressed people living with HIV (Neidleman et al 2020). In the current study, we describe a new approach called T-TRACE (TCR Tracing of Unperturbed Analogous Cell), that takes advantage of multi-omics single-cell analysis (by single-cell RNAseq, Antibody-seq, and TCR sequencing) and the fact that the reservoir is largely clonally expanded, and which allowed us to conduct full-transcriptome analysis of reservoir cells capable of inducing HIV gene expression.
**Methods:** CD4+ T cells from an ART-suppressed donor were enriched for reservoir cells through cell sorting and split into two fractions. One fraction was immediately processed for multi-omics analysis to generate the "atlas". The remaining fraction was stimulated with PMA/ionomycin for 40 hours, and then analyzed using the same multi-omics platform. Induced reservoir cells from the stimulated sample were defined as those harboring HIV transcripts. TCR sequences from these cells were matched to the atlas to identify clonally expanded, inducible reservoir cells in their baseline (pre-stimulated) state. These cells were then deeply interrogated by mining their transcriptomes and surface protein expression.
**Results:** We found 107 HIV+ cells from the stimulated sample. Mapping these cells to their clones in the atlas sample by T-TRACE identified 30 different clonotypes of HIV reservoir cells. Compared to total atlas cells, these reservoir cells preferentially expressed low levels of CD62L and high levels of cytolysis-associated transcripts (perforin, granulysin, granzyme). Multiple clonotypes of inducible reservoir cells harbored HIV transcripts at baseline (prior to stimulation), suggesting there is overlap between the inducible and transcriptionally-active reservoir.
**Conclusion:** T-TRACE allows full transcriptomic and surface phenotypic analysis of inducible, clonally-expanded reservoir cells in their original (non-stimulated) state. In-depth analysis of these reservoir cells revealed them to be primarily of a T effector memory phenotype (CD62Llo) and to exhibit a cytolytic signature. Future application of T-TRACE on specimens from additional donors, including from longitudinal sampling, will provide insights into mechanisms of HIV persistence and potentially identify biomarkers of the inducible reservoir.

## 331 CD4+ T-CELL SUBSET-SPECIFIC DIFFERENCES IN HIV LATENCY ESTABLISHMENT

New Investigator Scholar

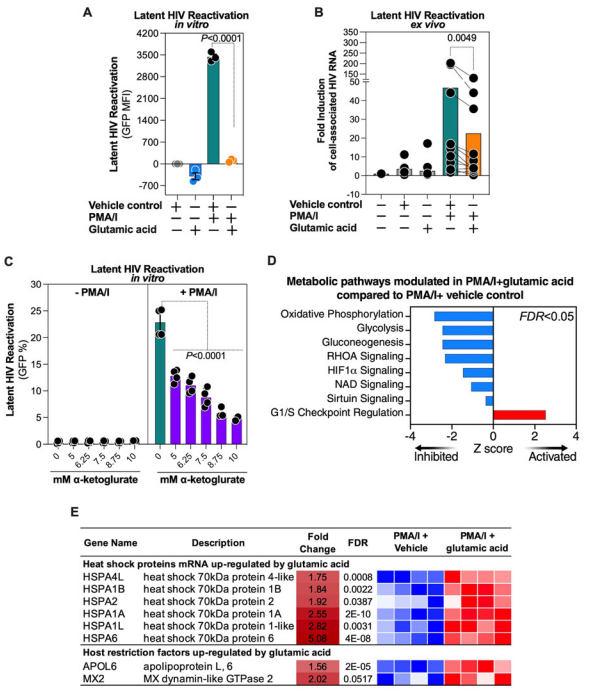
**Eun Hye G. Kim**[1], Lara Manganaro[2], Michael Schotsaert[1], Lubbertus C. Mulder[1], Viviana Simon[1]
*[1]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [2]Istituto Nazionale Genetica Molecolare, Milan, Italy*

**Background:** CD4 T cells are primary targets of HIV infection and contribute to life-long latency. Single-cell analysis of HIV latency is hampered by the difficulties identifying cells with transcriptionally silent proviruses. To better support multi-dimensional analyses, we used a HIV reporter virus, pLAI2-ΔE-Pro-Codes, to identify CD4 T cell subsets most prone to harboring LTR-silent provirus.
**Methods:** To distinguish latently or productively infected CD4 T cells, we used Pro-Codes reporter virus encoding V5-NGFR (LTR-independent expression) in the place of Env sequence and HSA-mCherry (LTR-dependent expression). The reporter viruses express a functional Nef. We infected primary human CD4 T cells stimulated with IL-2 or IL-2+α-CD3/CD28 with Pro-Codes pseudotyped with pSV III-92 HT 594.1 Env. Cells were analyzed by flow cytometry and CyTOF for latent vs. productive infection in seven different T cell subsets. Sorted latently and productively infected cells were analyzed for viral integration and transcription.
**Results:** Cells productively infected with Pro-Codes down-regulated CD4 while latently infected cells expressed CD4 at the same level as mock infected cells. Latent infection was confirmed by the presence of integrated proviruses but absence of multiple spliced transcripts in contrast to productive infection were both products were present. Phenotypic analysis by CyTOF and tSNE analysis revealed discrete CD4 T cell subsets with unique cytokine and cell marker profiles. All seven CD4 T cells subsets harbored more latently infected than productively infected cells. CD4 regulatory T cells (Tregs) and CD4 effector memory T cells (TEM) were most susceptible to latency establishment (7-10% LTR silent infection versus 2-5% LTR active infection). Productively infected cells expressed higher levels of CD69/HLA-DR while expression of these markers on latently infected cells was lower or equal to the expression on mock infected cells.
**Conclusion:** Our Pro-Codes reporter reliably identified latency at the single cell level. Our data show that LTR-silent infection is more frequent than productive infection in primary CD4 T cells and highlight the CD4 T cell subsets most permissive for LTR-silent infection. We describe a hierarchy of CD4 T cell subsets that support LTR-silent and LTR-active infection with up-regulation of CD69/HLA-DR being a hallmark for productive infection. This model system opens the door to studying how to best reactivate proviruses to purge the viral reservoir.

## 332 GLUTAMINOLYSIS ALTERS CD4+ T-CELL IMMUNOMETABOLISM AND INHIBITS HIV TRANSCRIPTION

**Leila B. Giron**[1], Toshitha Kannan[1], Jane Koshy[1], Clovis S. Palmer[2], Alan Landay[3], Andrew Kossenkov[1], Mohamed Abdel-Mohsen[1]
*[1]Wistar Institute, Philadelphia, PA, USA, [2]Burnet Institute, Melbourne, Australia, [3]Rush University, Chicago, IL, USA*

**Background:** We recently reported (Giron et al., Nature Comm. 2021) that the plasma levels of the metabolite glutamic acid predict a delayed time-to-viral-rebound and a higher probability of achieving a post-treatment controller phenotype after antiretroviral therapy (ART) interruption. Glutamic acid metabolism (glutaminolysis) can fuel the tricarboxylic acid (TCA) cycle through its conversion to α-ketoglutarate (α-KG), which modulates the cellular immunometabolic and epigenetic landscapes. We aimed to investigate the potential direct impact of glutamic acid and α-KG on latent HIV transcription in vitro and ex vivo.
**Methods:** The ability of glutamic acid and α-KG to inhibit PMA/I-mediated reactivation of latent HIV was evaluated in the J-Lat 5A8 HIV latency model (by flow cytometry), and in primary CD4+ T cells from 11 HIV-infected ART-suppressed individuals (by qPCR). Effects of glutamic acid on the transcriptome of primary CD4+ T cells from HIV+ ART+ individuals were evaluated by RNA-seq. Unpaired and paired t-tests were used for analyses and false discovery rates (FDR) were calculated to account for multiple comparisons.
**Results:** Our in vitro experiments show that both glutamic acid and α-KG inhibit PMA/I-mediated reactivation of latent HIV in the J-Lat HIV latency model ($P<0.0001$; Fig 1A-B). Consistently, in CD4+ T cells from HIV+ ART+ individuals, glutamic partially inhibited the ability of PMA/I to induce intracellular HIV RNA levels ($P=0.0049$; Fig 1C). Transcriptomic analyses revealed that, during PMA/I stimulation, glutamic acid inhibited several metabolic pathways that induce HIV transcription and replication including, oxidative phosphorylation (OXPHOS), glycolysis, HIF1α signaling, NAD signaling, and Sirtuin signaling (FDR<0.05; Fig 1D). In contrast, glutamic acid induced the mRNA expression of several proteins that suppress HIV transcription and replication, including the 70 kD heat shock proteins (HSP70) and the anti-HIV host restriction factors APOL6 and MX2 (FDR<0.05; Fig 1E).
**Conclusion:** Our data indicate that glutamic acid metabolism, a metabolic pathway previously associated with post-treatment control of HIV, may shift the immunometabolic status of CD4+ T cells to inhibit HIV transcription and replication. Future investigations are needed to understand the underlying mechanisms of how glutaminolysis may regulate HIV control during ART and/or post-ART cessation. This understanding may inform novel immunometabolic approaches to recapitulate the post-treatment controller phenotype.




E

| Gene Name | Description | Fold Change | FDR | PMA/I + Vehicle | PMA/I + glutamic acid |
|---|---|---|---|---|---|
| **Heat shock proteins mRNA up-regulated by glutamic acid** | | | | | |
| HSPA4L | heat shock 70kDa protein 4-like | 1.75 | 0.0008 | | |
| HSPA1B | heat shock 70kDa protein 1B | 1.84 | 0.0022 | | |
| HSPA2 | heat shock 70kDa protein 2 | 1.92 | 0.0387 | | |
| HSPA1A | heat shock 70kDa protein 1A | 2.55 | 2E-10 | | |
| HSPA1L | heat shock 70kDa protein 1-like | 2.82 | 0.0031 | | |
| HSPA6 | heat shock 70kDa protein 6 | 5.08 | 4E-08 | | |
| **Host restriction factors up-regulated by glutamic acid** | | | | | |
| APOL6 | apolipoprotein L, 6 | 1.56 | 2E-05 | | |
| MX2 | MX dynamin-like GTPase 2 | 2.02 | 0.0517 | | |

## 333 IDENTIFICATION OF THE HIV-1 Ast RNA DOMAINS INVOLVED IN PROMOTING VIRAL LATENCY

**Rui Li**[1], Kaveh Daneshvar[2], Biplab Paul[2], Michelle Pleet[3], Rachel Barclay[3], Isabella Caico[1], Zahra Gholizadeh[1], Mohd Shameel Iqbal[1], Fatah Kashanchi[3], Alan Mullen[2], Fabio Romerio[1]
*[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Harvard Medical School, Boston, MA, USA, [3]George Mason University, Fairfax, VA, USA*

**Background:** HIV-1 latency occurs via epigenetic modifications that lead to nucleosome assembly and transcriptional silencing of the proviral 5'LTR. HIV-1 expresses an antisense transcript (Ast) from a negative sense promoter within the 3'LTR. We reported that Ast recruits the Polycomb Repressor Complex 2 (PRC2) to the HIV-1 5'LTR, promoting trimethylation of lysine 27 on histone H3 (H3K27me3), nucleosome assembly and transcriptional silencing. Here, we sought to further dissect these events and to identify domains and motifs of Ast that play a role in promoting HIV-1 latency.

**Methods:** We generated a panel of Ast mutants, which we stably transduced into the Jurkat cell-based model of latency (Jurkat E4), which contain a GFP reporter for ease of measurement. We used a combination of functional and molecular assays to identify the domains and motifs of Ast that are involved in promoting HIV-1 latency. We also performed pull down and mass spectrometry studies to identify additional transcriptional and epigenetic silencers associated with Ast.

**Results:** We found that the U3 sequence of Ast (376 nucleotides at the 5' end) mediates its interaction with the homologous U3 region of the proviral 5'LTR. We also identified two polypyrimidine motifs in the U3 sequence of Ast that are critical for this interaction. Further, we found that a 70-nt sequence within Ast RNA contains a putative G-quadruplex motif involved in the interaction with PRC2. Disruption of the polypyrimidine and G-quadruplex motifs inhibits the latency-promoting activity of Ast. Interestingly, we found that other regions of Ast also had an impact on its function, suggesting that full Ast suppressive activity may require interaction with additional factors. Indeed, fractionation of cell lysates by size-exclusion chromatography showed that Ast elutes exclusively in high molecular weight fractions (>2.2 MDa). In addition, mass spectrometry (MS)-based analysis of the Ast RNA interactome identified several host transcription repressors and epigenetic silencers known to suppress HIV-1 transcription. We used RNA immunoprecipitation to validate the interaction between Ast and some of the host factors identified by MS.

**Conclusion:** These studies provide molecular and functional evidence that the HIV-1 antisense transcript Ast promotes viral latency by bridging PRC2 and additional host factors to the 5'LTR, leading to its transcriptional suppression. These results further support the use of Ast RNA in the context of 'block and lock' HIV-1 cure strategies.

## 334 HIV LATENCY REVERSAL VIA IAP ANTAGONISM AND TARGETED BET BROMODOMAIN INHIBITION

**Shane D. Falcinelli**[1], Jackson Peterson[1], Anne-Marie Turner[1], David Irlbeck[2], Samuel Raines[1], Katherine James[1], Cameron Sutton[1], Anthony Sanchez[1], Edward P. Browne[1], Richard M. Dunham[2], Nancie Archin[1], David M. Margolis[1]
*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]ViiV Healthcare, Research Triangle Park, NC, USA*

**Background:** Accelerating reservoir decay through reversal of HIV latency and clearance of infected cells may facilitate an HIV cure. Recent preclinical studies have demonstrated that non-canonical NF-κB agonists (IAP antagonists, IAPi) induce unprecedented levels of proviral expression without toxicity during suppressive ART in two animal models of latent SIV/HIV infection. However, combination approaches may be needed to fully target the latent reservoir.

**Methods:** We conducted a targeted screen of mechanistically distinct latency reversal agents that might enhance HIV proviral expression induced by IAPi in a Jurkat model of latency, and identified strong combination activity with bromodomain and extraterminal domain protein inhibitors (BETi). Mechanistic investigations using CRISPR-Cas9 and scRNAseq were undertaken to identify host proteins responsible for the combination activity. Based on this analysis, we evaluated the ability of both pan- and selective-BET antagonism to reverse latency in primary CD4 T cells from ART-suppressed HIV seropositive participants. Latency reversal was assessed using digital PCR for multiple HIV RNA species, ultrasensitive p24 digital ELISA, and quantitative viral outgrowth assays.

**Results:** IAPi/BETi resulted in profoundly synergistic induction of proviral expression. Mechanistic investigations demonstrated a primary role for the BET protein BRD4 in the IAPi/BETi combination activity and a dependence on NF-κB sites in the HIV promoter. Given that pan-BETi have significant dose-limiting toxicities, we conducted ex vivo evaluations of both pan- and selective-BET targeting approaches. There was robust induction of cell-associated gag HIV RNA transcripts for IAPi+BETi but not IAPi+BET degraders. Surprisingly however, even for the IAPi/BETi combination there was only modest evidence of induction of tat-rev transcripts, HIV p24 protein or viral outgrowth relative to T cell activating agents.

**Conclusion:** Overall, this study provides evidence to support further testing of the IAPi/BETi combination in preclinical animal models of HIV latency, further defines the role of BET proteins in HIV latency, and highlights HIV splicing and full transcriptional elongation as important targets for future latency reversal agent development.

## 335 HIV-INDUCED TYPE I INTERFERONS PROMOTE VIRAL LATENCY IN INFECTED MACROPHAGES

**Timothy Hanley**[1], Laura J. Martins[1], Vicente Planelles[1]
*[1]University of Utah, Salt Lake City, UT, USA*

**Background:** The existence of latent HIV reservoirs, consisting of both T cells and myeloid cells, represents the major obstacle to viral cure. There remain crucial gaps in our understanding of the molecular mechanisms that lead to latent infection in myeloid cells. We hypothesize that HIV-induced type I IFN signaling promotes a state of transcriptional latency in HIV-1 infected macrophages.

**Methods:** We examined HIV-1 replication kinetics and the effects of type I IFN signaling on HIV-1 replication in an in vitro monocyte-derived macrophage (MDM) model. Transcription factor recruitment to the 5' LTR was evaluated using chromatin immunoprecipitation (ChIP). Chromatin structure at the promoter was assessed by restriction enzyme accessibility. Single cell RNA sequencing (scRNA-Seq) was utilized to determine changes in gene expression in infected macrophages. The contribution of innate immune receptors to latency was determined using shRNA.

**Results:** We show that HIV-1 replication peaks early after infection in monocyte-derived macrophages (MDMs) and steadily decreases over time. This decrease correlates with decreased viral transcription, suggesting that HIV-1 enters a latent state in at least a subset of infected cells. The transition to latency is associated with changes in both transcription factor recruitment to the viral promoter and nucleosome assembly at the transcription start site. Comparing productively-infected MDMs to latently-infected MDMs using scRNA-Seq reveals differential expression of a number of IFN-regulated genes (IRGs). In addition, blocking type I IFN signaling reverses the transition to latency, suggesting that type I IFNs produced by infected MDMs contribute to the repression of viral

replication over time. This transition from productive to latent infection requires signaling through the MAVS-TBK1 pathway. Finally, the viral accessory protein, Vpr, induces a suboptimal IFN response that contributes to the establishment of viral latency.

**Conclusion:** Our data suggest that HIV-1 infection in MDMs induces type I IFN expression via MAVS-TBK1 signaling which promotes a state reminiscent of viral latency. These findings identify a key signaling pathway involved in the establishment of HIV-1 latency and may uncover possible targets for preventing or reversing latency in this critical viral reservoir.

## 336 SMYD5 ACTIVATES HIV-1 TRANSCRIPTION AND IS UPREGULATED BY Tat AND USP11

**Daniela Boehm**[1], Victor L. Lam[2], Melanie M. Ott[1]
*[1]Gladstone Institutes, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA*

**Background:** Despite great efforts, "shock and kill" approaches have so far failed to significantly reduce the size and impact of latent HIV-1 reservoirs. There is a need to develop alternative, possibly complementary, strategies to "shock and kill" to achieve durable viral control in the absence of antiretroviral therapy (ART). Transcriptional silencing in latency research is a relatively new concept. Many transcriptional regulators for HIV-1 have been identified. Besides histone deacetylation, a growing list of methyl transferases (MTs) and demethylases indicates that methylation of DNA, histones and non-histone proteins is essential for HIV-1 transcriptional regulation. Our working hypothesis is that co-activating MTs play a critical role in preventing permanent silencing of the HIV-1 locus. The rationale is that co-activating KMTs by methylating histones or Tat facilitate transcription initiating, thereby directly antagonizing repressive epigenetic mechanisms necessary for durable silencing of the HIV-1 locus.

**Methods:** We performed a comprehensive lentiviral shRNA screen of human lysine methyltransferases (KMTs) in J-Lat cells to identify new activators and repressors of HIV transcription. The top activating KMT SMYD5 was validated in primary CD4+ T cell experiments. To identify the mechanism underlying how SMYD5 contributes to HIV latency we performed luciferase assays, chromatin- and co-immunoprecipitation experiments, in vitro methylation and electrophoretic mobility shift (EMSA) assays.

**Results:** In an RNAi-based screen of human lysine methyltransferases we identified the SET and MYND domain-containing protein 5 (SMYD5), which was previously reported to target lysine 20 at histone H4 (H4K20me3), as a co-activator of HIV transcription. Knockdown of SMYD5 suppresses HIV-1 transcription in latently infected T-cell lines and primary CD4+ T cells. SMYD5 is recruited to the HIV-1 promoter upon activation, binds TAR RNA and interacts with Tat. We also provide evidence that SMYD5 is stabilized by Tat through the deubiquitinase USP11.

**Conclusion:** We propose that SMYD5 is a new host activator of HIV-1 transcription stabilized by Tat and USP11 and together with USP11 a possible target for latency-promoting therapy.

## 337 CIRCADIAN-MODULATING COMPOUNDS INDUCE HIV REACTIVATION FROM LATENTLY INFECTED CELLS

New Investigator Scholar

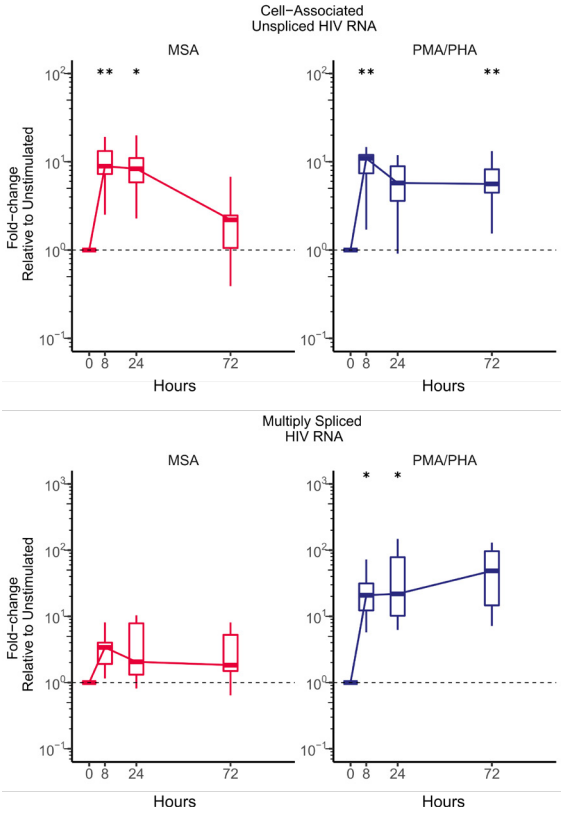
**Jared Stern**[1], Jennifer Zerbato[1], Ajantha Rhodes[1], Sharon Lewin[1], Michael Roche[1]
*[1]Peter Doherty Institute, Melbourne, Australia*

**Background:** In people living with HIV (PLHIV) on antiretroviral therapy (ART), persistent latent HIV is a major barrier to a cure. We and other have shown that cell-associated unspliced (CA-US) HIV RNA is always detected in CD4+ T-cells from blood from PLHIV on ART and this varies with time. Given our previous work showing that the circadian transcription factors, Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle Arnt-like protein-1 (BMAL1), bind to the HIV long terminal repeat (LTR) and increase HIV transcription, we hypothesised that modulation of circadian proteins could increase HIV transcription and reverse latency.

**Methods:** Circadian-modulating compounds were evaluated for activation of the LTR in the latently infected cell line, J-Lat Tat-IRES-GFP clone A2. Toxicity and reactivation were measured by flow cytometry and by qPCR for CA-US HIV RNA. Best-hit candidates were further assessed in full-length J-Lat clone 10.6 and ACH2, and CD4+ T-cells isolated from peripheral blood mononuclear cells from PLHIV on ART. Both J-Lat clones express green fluorescent protein (GFP) following activation of the LTR. CD38, HLA-DR and CD69 expression were quantified by flow cytometry. Circadian gene expression was assessed by RT-qPCR.

**Results:** Two organic selenium compounds, L-methylselenocysteine (MSC) and methaneseleninic acid (MSA), known to increase Bmal1 transcription and translation, increased the mean±sd fold GFP expression in J-Lat A2 by 68.9±0.43 and 39.05±5.66, with half maximal effective concentrations ($EC_{50}$) of 78.4uM and 8nM respectively. 10uM MSA increased GFP expression in J-Lat 10.6 by 19.8-fold (p=0.09) and expression of p24 in ACH2 by 4.25-fold (p=0.009). MSA had little toxicity in CD4+ T-cells from PLHIV (76.3% viable, p=0.008) and induced CA-US HIV RNA expression 2.5-19.9-fold above baseline (p=0.008). Bmal1 expression increased 13.74-fold (p=0.02) in ACH2 cells and 2.28-fold (p=0.008) in primary CD4+ T-cells. MSA increased CD69 expression from median 2.2% to 36.9% (p=0.03), while CD38 expression decreased from 41% to 2.2% (p=0.03).

**Conclusion:** The organic selenium compound MSA reactivated HIV transcription and translation in several latently infected cell lines, as well as reactivating viral transcription in cells from PLHIV. A robust induction of Bmal1 expression was observed early after MSA stimulation, indicating direct effects on BMAL1. The innate circadian control of basal HIV transcription on ART offers a novel druggable target for the shock and kill cure strategy.




## 338 PHARMACOLOGIC CONTROL OF CD4+ T-CELL PROLIFERATION TO TARGET HIV-1 PERSISTENCE

**Emily A. Innis**[1], Callie Levinger[2], Matthew A. Szaniawski[1], Elizabeth S. Williams[1], José Alcamí[3], Alberto Bosque[2], Joshua Schiffer[4], Mayte Coiras[3], Adam Spivak[1], Vicente Planelles[1]
*[1]University of Utah, Salt Lake City, UT, USA, [2]George Washington University, Washington, DC, USA, [3]National Center of Microbiology (CNM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain, [4]Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

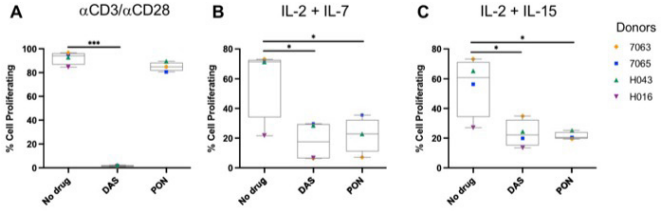
**Background:** The major barrier to eradication of human immunodeficiency virus 1 (HIV-1) is the presence of a latent reservoir of HIV-1 infected quiescent CD4+ memory T cells. Despite effective antiretroviral therapy (ART), this latent reservoir persists over time due to proliferation of these cells. Memory CD4+ T cells can proliferate through two mechanisms; homeostatic proliferation via γc-cytokines or antigen-driven proliferation. We hypothesize that therapeutic modalities that block homeostatic and antigen-driven proliferation can lead to the reduction of the latent HIV-1 reservoir.

**Methods:** We screened a library of FDA-approved oncology drugs and determined their efficacy as anti-proliferative agents that block homeostatic

and/or antigen-driven proliferation of memory CD4+ T cells. We isolated memory CD4+ T cells from peripheral blood mononuclear cells (PBMCs) and used a cell tracer dye to track proliferation by flow cytometry. Cells were stimulated with IL-7 to induce homeostatic proliferation or αCD3/αCD28 beads to induce antigen-driven proliferation. We confirmed top hits in memory CD4+ T cells from people living with HIV-1 (PLWH). We also interrogated downstream signaling of γc-cytokine stimulation to determine mechanism of action via flow cytometry. Lastly, we evaluated the effect of drugs on spontaneous reactivation from cells from PLWH using an ultrasensitive p24 ELISA immunoassay. Statistical analysis was performed using Graph Pad Prism and comparisons between control and drug treatments were made using a paired two-tailed T test and ANOVA test. Mean and ± s.d. are considered.

**Results:** We found that tyrosine kinase inhibitors dasatinib and ponatinib, and trametinib, a MEK inhibitor, reduced both antigen-driven and homeostatic proliferation by at least 65% without dramatically reducing viability. In memory CD4+ T cells from PLWH, only dasatinib reduced both antigen-driven and homeostatic proliferation and prevented spontaneous rebound of HIV-1 virus. We also found that dasatinib blocks STAT5-phosphorylation to restrict homeostatic proliferation induced by IL-2 plus IL-7.

**Conclusion:** Our results establish that the anti-cancer drug and tyrosine kinase inhibitor, dasatinib, is a promising candidate to be used as an anti-proliferative drug in a clinical trial. Dasatinib efficiently blocks proliferation and spontaneous reactivation and is already well tolerated in patients with chronic myeloid leukemia




**Dasatinib curtails antigen-driven and γc cytokine induced proliferation of CD4+ memory T cells from people living with HIV-1 on suppressive ART.** Memory CD4+ T cells from people living with HIV-1 (represented by different colored symbols) were kept under ART (Nelfinavir 1uM) for the duration of the experiment to prevent viral spread and stimulated with **A.** αCD3/αCD28 beads, **B.** IL-2+IL-7, or **C.** IL-2+IL-15 and treated with dasatinib or ponatinib at 100nM as described in Figure 3. Each experimental group contains data from four donors (n=4) with the exception of ponatinib (n=3). Analysis by flow cytometry was performed to assess proliferation. Error bars, mean ± s.d. All differences between means with $p < 0.05$ are indicated across categories. *, p ≤ 0.05 ; **, p ≤ 0.01; ***, p ≤ 0.001; not significant without stars.

## 339 IRF7 REGULATES HIV-1 LATENCY REVERSAL INDEPENDENT OF CYTOKINE SIGNALING BLOCKADE

New Investigator Scholar

**Ifeanyi J. Ezeonwumelu**[1], Edurne Garcia-Vidal[1], Bruna Oriol-Tordera[1], Marta Ruiz-Riol[1], André Gohr[2], Marta Massanella[1], Bonaventura Clotet[1], Roger Badia[1], Eva Riveira-Muñoz[1], Ester Ballana[1]
*[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany*

**Background:** The mechanisms governing HIV persistence remain to be fully elucidated. Understanding these mechanisms is key for developing successful strategies that aim to target and eliminate the viral reservoir, and ultimately cure HIV infection. Increasing interest has focused on targeting the immune response to HIV latent infection, including modulation of the JAK/STAT pathway, which plays a crucial role in mediating innate immune responses. Here, we show that IRF7 drives HIV latency reversal by a subclass of Janus kinase inhibitors (JAKinibs).

**Methods:** Non-clonal GFP-expressing myeloid (HL60) and lymphoid (Jurkat) in vitro models of HIV-1 latency were used to evaluate the reactivation capacity of distinct JAKinibs (n=10) by flow cytometry (FC). Immunophenotyping of ex vivo treated CD4+T cells from uninfected donors and ART-suppressed HIV+ study participants were performed by multicolour FC and latency reactivation measured by qPCR amplification of supernatant HIV-1 RNA. RNAseq of in vitro JAKinib-treated cells was performed for whole transcriptome profiling. qPCR and western blot were used to validate gene and protein expression and further characterize signalling pathways.

**Results:** A subclass of selective JAK2inibs (2/8), including fedratinib, consistently reversed HIV-1 latency in all tested in vitro models (p<0.001). Fedratinib ex vivo treatment of HIV+ CD4+T cells resulted also in significant HIV reactivation compared to untreated control, without major changes in immune cell activation, but presenting an increased percentage of effector memory and central memory CD4+T populations. Whole transcriptomic profiling supported reactivation data, showing common gene expression signatures between LRA treated cells (fedratinib and PMA) in contrast to other JAKinibs, albeit fedratinib presented significantly fewer affected gene sets in the pathway analysis. Interestingly, we observed a significant induction of IRF7 expression upon fedratinib treatment (6-fold, p<0.001), despite the blockade of the JAK/STAT pathway and downregulation of proinflammatory cytokines and chemokines. Moreover, IRF7 expression positively correlated with latency reversal capacity by JAK2inibs (rho=0.86, p=0.006) and other LRAs. siRNA knockdown of IRF7, but not JAK2, limited HIV reactivation (p=0.005), further demonstrating the role of IRF7 in HIV latency.

**Conclusion:** Our findings indicate that IRF7 could be an important modulator of HIV-1 latency and might play a crucial role in HIV-1 eradication strategies.

## 340 NFκB BINDING MOTIF GENOTYPES IN PROVIRAL PROMOTERS ACROSS HIV-1 SUBTYPES

**Ha Eun Lim**[1], Pragya Khadka[1], Erika Benko[2], Colin Kovacs[2], Ronald Galiwango[3], Paul Buule[3], Taddeo Kityamuweesi[3], Andrew Redd[4], Steven J. Reynolds[4], Thomas Quinn[4], Jessica Prodger[5], R Brad Jones[1], Guinevere Q. Lee[1]
*[1]Weill Cornell Medicine, New York, NY, USA, [2]Maple Leaf Medical Clinic, Toronto, Canada, [3]Rakai Health Sciences Program, Kalisizo, Uganda, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]University of Western Ontario, London, Canada*

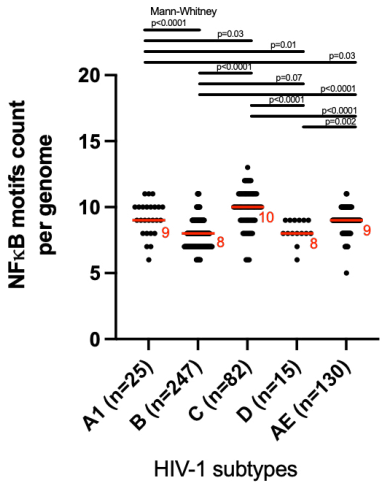
**Background:** NFκB binds to the HIV promoter and is one of the major classes of human transcription factors that activates HIV transcription. HIV also has a high mutation rate, which can result in the gain/loss of binding sites. Here, we hypothesize that five distinct HIV-1 strains: subtype A1, B, C and D and AE, in genome-intact versus defect proviruses within-hosts, differ in NFκB binding site genotypes, which could imply different likelihoods of viral transcriptional activation.

**Methods:** Viral promoter sequences were retrieved from the Los Alamos HIV Sequence database (A1 n=25, B n=247, C n=82, D n=15, AE n=130). In addition, since integrated viral DNA are often defective and non-replication-competent, we sequenced proviruses from chronically HIV-infected and virologically-suppressed donors (subtype B 615 genomes 15 donors, subtype D 113 genomes 9 donors, AE 89 genomes 2 donors) and compared intact-vs-defective genomes within-hosts. An in-house software, NFcount, was developed to screen for NFκB binding motifs, defined as the canonical H, C and F sites, in addition to a list of non-canonical motifs previously identified experimentally and via a single nucleotide mutation matrix model (Du 2014).

**Results:** HIV-1 subtype A1, C, sand AE all had significantly more NFκB binding motifs relative to subtype B and D (all p<0.0001 Mann-Whitney, Figure 1). Our in-house sequencing results revealed that within each infected individual, NFκB motif counts were not different between intact versus defective viral genomes (all p>0.05) except for hypermutated genomes associated with host defense proteins APOBEC-3G/3F activities (all p<0.0001); hypermutation did not eliminate but resulted in 33-50% reduction of median site counts (subtype B from 9 to 6, D from 7 to 4, AE from 8 to 4). Finally, even within a given viral subtype, median counts were significantly different across donors (B p<0.0001, D p<0.0001, AE p<0.0001, Kruskal-Wallis or Mann-Whitney).

**Conclusion:** NFκB motif counts significantly differed across HIV-1 subtypes and across infected individuals within a subtype. Along with other factors such as chromosome accessibility, NFκB motif counts and genotypes can contribute to varying likelihoods of viral transcriptional activation, which may in turn impact time-to-virologic-rebound in the absence of treatment and should be explored in future studies.

**Figure 1. NF-kappaB binding motif counts.** Counts were significantly different across the five HIV-1 strains evaluated in this study, suggesting different likelihoods of viral transcription activation across viral subtypes. Red horizontal lines indicate median values.




## 341 IDENTIFICATION OF SYNERGISTIC COMBINATIONS OF HIV SILENCING PROMOTING FACTORS

**Zichong Li**[1], Warner Greene[1]
[1]*Gladstone Institutes, San Francisco, CA, USA*

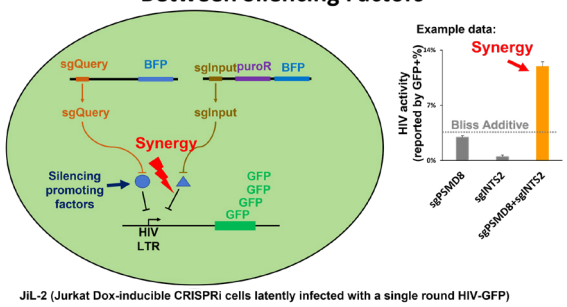
**Background:** The activity of latent HIV is counter-regulated by both silencing and activating factors. To durably silence latent HIV ("block-and-lock"), we will specifically define how to enhance the activity of synergistic repressors while neutralizing HIV activators in relevant host cells. In this research, we are systematically evaluating the combinations of recently identified silencing promoting factors (SPFs) or inhibitors of activators for synergistic proviral silencing. We will also evaluate persistence of silencing when factors/inhibitors are removed––a critical hurdle we must clear for success of the block and lock strategy.

**Methods:** To evaluate synergistic SPFs, we developed an inducible CRISPRi platform in HIV-GFP-latently-infected Jurkat cells. This system contains two lentiviral sgRNA vectors with different selection markers for introducing a pair of sgRNAs that target two SPFs. Using this platform, we evaluated the combinations among a selected set of 8 SPFs to assess whether synergistic networks of factors existed. Bliss-independence tests were used to validate synergy. We then conducted a proof of concept to use the network to discover synergies between the existing factors and drugs and repurpose them to block HIV.

**Results:** Seventeen synergies involving 8 SPFs have been identified. Among them, sgINTS2 (Integrator subunit) strongly synergizes with sgPSMD8 and sgFTSJ3 (previously reported to inhibit CDK9/SEC). This led us to focus on Protein Phosphatase IIa, which interacts with and mediate the silencing promoting activity of Integrator. Small molecule activator of PP2A (SMAP-2) and CDK9/SEC inhibitors synergistically silenced HIV. Knockdown of several PP2A regulatory subunits revealed that loss of STRN4 markedly activated latent HIV, indicating STRN4's key role in PP2A-induced HIV silencing.

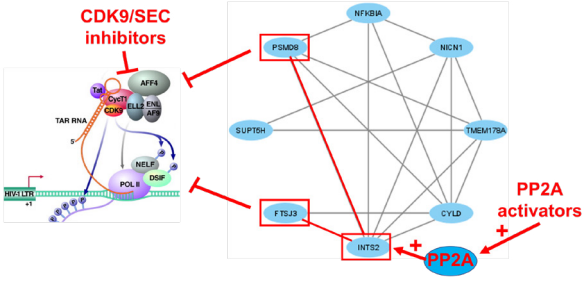
**Conclusion:** We established a flexible platform for assessing synergistic activities between SPFs. We find PP2A activators synergizing with CDK9/SEC inhibitors promoting silencing of latent HIV. Further, we identified the STRN4 regulatory subunit of PP2A as a key mediator of this silencing response. We will use this platform to identify additional synergies between SPFs and evaluate their ability to silence HIV in primary CD4 T cell latency models and in cells from HIV-infected patients on ART. We will also explore sequence-specific delivery of these synergistic repressors to sites of HIV provirus integration.

**A Platform to Identify Synergistic Interactions Between Silencing Factors**




JiL-2 (Jurkat Dox-inducible CRISPRi cells latently infected with a single round HIV-GFP)

**Synergies Among SPFs and Prior Knowledge Leading to Novel Drug Combinations**




## 342 MiRNA-103 MODULATES CCR5 AND AFFECTS ESTABLISHMENT OF HIV-1 LATENCY IN CD4+ T CELLS

New Investigator Scholar

**Nicolas Bellini**[1], Robert Lodge[1], Tram N. Pham[1], Jaspreet Jain[1], Cécile Tremblay[2], Jean-Pierre Routy[3], Alon Herschhorn[4], Thomas T. Murooka[5], Eric A. Cohen[1]
[1]*Institut de recherches cliniques de Montréal, Montréal, Canada,* [2]*Centre de Recherche du CHUM, Montreal, Canada,* [3]*McGill University Health Centre, Montreal, Canada,* [4]*University of Minnesota, Minneapolis, MN, USA,* [5]*University of Manitoba, Winnipeg, Canada*

**Background:** It has been proposed that activated-to-memory transitioning CD4+ T cells can harbor latent HIV-1, due to a brief transient increase in CCR5 co-receptor expression and their reduced ability to transcribe integrated proviral DNA. Recently, we identified miRNA-103, a non-coding RNA regulated by p53, as a modulator of CCR5 in macrophages. We postulated that miRNA-103 could also regulate CCR5 in CD4+ T cells.

**Methods:** CD4+ T cells were isolated from peripheral blood mononuclear cells (PBMCs) of healthy individuals and those living with HIV. CCR5 mRNA and miRNA-103 expression were measured by RT-qPCR. Nucleofection of control, miRNA-103 mimic or inhibitor in lymphocytes were performed prior to evaluating the levels of CCR5 mRNA and surface expression or the degree of CCR5-dependent HIV entry. Primary CD4+ T cells were infected with the dual reporter virus HI.fate.E and latently/productively infected CD4+ T cells were identified by flow cytometry based on E2-Crimson (under HIV LTR) and ZS-Green (under the EF1α promoter).

**Results:** First, we show that mRNA and surface protein levels of CCR5 are negatively correlated with miRNA-103 levels in CD4+ T cells. Moreover, miRNA-103 mimics decreased mRNA CCR5 levels (FC=0.42x) and reduced CCR5-dependent HIV-1 infection (FC=0.26x) compared to control. Conversely, miRNA-103 inhibitors increased CCR5 expression in activated-to-memory transitioning CD4+ T cells (FC=3.4x). Interestingly, Nutlin-3, which upregulates p53, enhances miRNA-103 levels (FC=2.7x) and consequently, decreases CCR5 mRNA (FC=0.36x). Using HI.fate.E virus, we show that Nutlin-treated cells are less susceptible to either productive (FC=0.39x) or latent (FC=0,53x) CCR5-dependent infection compared to vehicle-treated cells. This suggests that sustained expression of miRNA-103 in CD4+ T cells may contribute to limit the establishment of the HIV-1 reservoir. Lastly, we demonstrate that CD4+ T cells from elite controllers (ECs) and viremic controllers (VCs) have less CCR5 mRNA and display an uptrend of miRNA-103 compared to ART-naïve progressors. Moreover, in these individuals, we observed a negative correlation (r=-0.42, p=0.04) between mRNA CCR5 and miRNA-103, irrespective of HIV progression states.

**Conclusion:** Overall, our findings strongly indicate that miRNA-103 contributes to the regulation of CCR5 expression in vivo. It is conceivable that by inhibiting the transient increase of CCR5 in activated-to-memory transitioning T cells, miRNA-103 can counter the establishment of HIV-1 reservoirs.

## 343 POTENT TARGETED ACTIVATOR OF CELL KILL (TACK) MOLECULES ELIMINATE HIV-INFECTED CELLS

**Carl J. Balibar**[1], Daniel J. Klein[1], Beata Zamlynny[1], Tracy L. Diamond[1], Zhiyu Fang[1], Carol Cheney[1], Marina Bukhtiyarova[1], Yangsi Ou[1], Min Xu[1], Abdellatif ElMarrouni[1], John F. Fay[1], Shih Lin Goh[1], Daria Hazuda[1], Bonnie Howell[1], Antonella Converso[1]
*[1]Merck & Co, Inc, Kenilworth, NJ, USA*

**Background:** Strategies to address both latent and virus expressing cells that contribute to viral recrudescence upon ART cessation are required to achieve functional cure in people living with HIV-1 (PLWH). Some non-nucleoside reverse transcriptase inhibitors (NNRTIs) have a weak secondary activity that results in selective cytotoxicity by promoting dimerization of HIV-1 Gag-Pol and intracellular activation of HIV-1 protease at concentrations that exceed clinically relevant exposures. Focusing on this secondary activity, we invented potent targeted activator of cell kill (TACK) molecules that selectively eliminate HIV-1 infected cells.
**Methods:** Using a phenotypic assay, we interrogated 6628 compounds that target the NNRTI binding site of HIV-1 reverse transcriptase (RT) for their ability to selectively kill HIV+ cells. Chemical optimization led to invention of potent TACK molecules. These were characterized in biochemical, biophysical, and cell-based assays to better understand their unique mechanism of action.
**Results:** Although 68% of tested compounds from a library of diverse NNRTI-related analogues had antiviral $IC_{50}$s <0.3 µM, TACK activity was uncommon, with only 1.7% of the library compounds yielding >50% HIV-1 infected cell killing at 0.3 µM. Optimization of promising leads yielded Pyr01, which exhibits comparable TACK potency and early-stage antiviral activity ($EC_{50}$ 27.5 ± 12.0 nM vs $IC_{50}$ 39.7 ± 6.2 nM, respectively). This represents a greater than 1000-fold improvement in TACK activity compared to the structural analogue Pyr02 ($EC_{50}$ 34400 ± 2820 nM), which has similar antiviral potency ($IC_{50}$ 131 ± 38.0 nM). Cocrystal structures of each compound bound to the RT-p66/p51 heterodimer revealed little difference in the interaction between Pyr01 and Pyr02 and the NNRTI site of RT-p66 or the conformation of residues located at the heterodimer interface. However, Pyr01 potently induced dimerization of RT-p66 ($EC_{50}$ 24.0 ± 2.7 nM) whereas Pyr02 did not ($EC_{50}$ 3634 ± 643 nM), an activity that results from the ability to bind to monomeric RT-p66. Pyr01 retained antiviral activity against a panel of 25 NNRTI resistance-associated variants and selectively eliminated HIV-1 infected CD4+ T-cells from PLWH on suppressive ART following reactivation ex vivo.
**Conclusion:** We invented mechanistically novel bifunctional NNRTIs with dually potent HIV-1 infected cell kill and antiviral properties, highlighting a new approach for viral reservoir reduction and HIV-1 cure strategies.

## 344 GENOME-WIDE CRISPR INHIBITION SCREEN IDENTIFIES A NEW HIV-1 SILENCING FACTOR SLTM

**Rachel Kim**[1], Savannah F. Pedersen[1], Jack A. Collora[1], Ya-Chi Ho[1]
*[1]Yale University, New Haven, CT, USA*

**Background:** HIV-1 persistence in latent reservoirs remains a major obstacle to cure. We postulate that HIV-1 silencing factors suppress HIV-1 reactivation, and inhibition of HIV-1 silencing factors will increase HIV-1 reactivation and guide drug designs.
**Methods:** We conducted a genome-wide CRISPR-inhibition (CRISPRi) screen on four Jurkat T cell clones having stably integrated HIV-1-GFP reporter with known integration sites in introns of actively transcribed genes. The four established HIV-1-GFP-infected Jurkat T cell clones were first transduced with dCas9-Krab (inhibitory domain) as CRISPRi-ready, HIV-1-infected cell lines then transduced with a pooled lentiviral genome-wide gRNA library (5 gRNAs/gene for 18,905 genes). As inhibiting HIV-1 silencing factors should increase HIV-1 expression, we identified cells having higher levels of HIV-1-GFP expression by flow cytometric sorting. gRNAs enriched in HIV-1-GFP+ cells were captured by targeted deep sequencing. The level of gRNA enrichment was calculated by MAGeCK and RIGER. To validate our results, we transduced three CRISPRi-ready Jurkat T cell clones with gRNAs targeting candidate HIV-1 silencing factors. A non-targeting gRNA served as negative control to measure baseline HIV-1-GFP expression. We measured cellular factor knockdown efficiency by qRT-PCR and western blot, and HIV-1-driven GFP expression by flow cytometry.
**Results:** The CRISPRi screen identified seven HIV-1 silencing factors (SLTM, SAFB, DBR1, DIS3, EXOSC4, NELFCD, and CYLD), which are significantly enriched in HIV-1-GFP+ cells ($P<0.05$ by MAGeCK and $P<0.001$ by RIGER) in 4 cell line clones. Of note, SAFB, NELFCD, and CYLD are known to inhibit HIV-1 expression, suggesting that our screen can identify HIV-1 silencing factors. In validation studies, CRISPRi-mediated knockdown of SLTM resulted in significant increases in HIV-1-GFP expression in three cell lines (4.2X in 1D7: 19.0% versus 4.5% baseline, P=0.005; 3.7X in 1G2: 22.9% versus 6.2% baseline, P=0.006; 1.9X in 8B10: 44.9% versus 23.7% baseline, P=0.004 by Student's t-test). Of note, SLTM is a transcription modulator having both DNA and RNA binding capacity not previously known to affect HIV-1 transcription.
**Conclusion:** Using a CRISPRi screen on Jurkat T cell clones harboring stably integrated HIV-1 proviruses, we identified SLTM as a new HIV-1 silencing factor and a new therapeutic target for HIV-1 latency reversal or epigenetic silencing.

## 345 DASATINIB PREVENTS HIV INFECTION OF MACROPHAGES AND REDUCE THE INFLAMMATORY POTENTIAL

**Sara Rodríguez-Mora**[1], Guiomar Casado[1], Lorena Vigón[1], Juan Cantón De Seoane[2], Fernando Ramos-Martín[1], Miguel Cervero[2], María Aranzazu Murciano-Antón[3], Adam Spivak[4], José Alcamí[1], Vicente Planelles[4], Mayte Coiras[1]
*[1]Instituto de Salud Carlos III, Majadahonda, Madrid, Spain, [2]Hospital Universitario Severo Ochoa, Madrid, Spain, [3]Centro de Salud Dr Pedro Laín Entralgo, Alcorcón, Spain, [4]University of Utah, Salt Lake City, UT, USA*

**Background:** Monocyte-derived macrophages (MDMs) contribute to long-lived HIV-1 reservoirs. MDMs also release soluble factors that contribute to the chronic inflammation in HIV+ individuals. Our group previously demonstrated that tyrosine kinase inhibitor (TKI) dasatinib, but not imatinib, prevents HIV-1 infection of CD4+ T lymphocytes. In this proof-of-concept study, we analyzed whether dasatinib or imatinib also protect MDMs from HIV-1 infection and/or reduce their inflammatory potential.
**Methods:** CD14+ cells isolated from PBMCs of ART-treated individuals with chronic HIV-1 infection (n=15) and healthy donors (n=11) were differentiated to MDMs for 5 days and then infected with JR_FL_Renilla strain for 48h in the presence or not of dasatinib 50nM or imatinib 10µM. HIV-1 infection was analyzed by chemiluminiscence and flow cytometry (antip24 kc57). SAMHD1 phosphorylation and synthesis of IFNγ and TNFα after stimulation with lipopolysaccharide were analyzed by flow cytometry. Cell viability was determined by microscopy and flow cytometry.
**Results:** 1) HIV+ individuals had undetectable viral load, 80% were men and 66.7% were MSM, median age was 67 years (IQR 45.5-71.3), CD4 and CD8 counts were 761 and 910 cells/mm3, respectively, and CD4/CD8 ratio was 0.98. 2) Dasatinib reduced 2.4- (p=0.0006) and 5.9-fold (p=0.0577) HIV-1 infection in MDMs from HIV-infected individuals and healthy donors, respectively (Fig.1A), whereas imatinib reduced the infection 1.2- and 1.7-fold, respectively. 3) Dasatinib reduced 1.8- (p=0.0420) and 2.6–fold (p=0.0459) SAMHD1 phosphorylation in MDMs from HIV+ individuals and healthy donors, respectively (Fig.1B), whereas imatinib did not cause significant changes. 4) IFNγ production decreased 3.0- (p=0.0104) and 2.1-fold from MDMs of HIV+ individuals and healthy donors treated with dasatinib, respectively (Fig.1C), while imatinib showed no significant effect. 5) The synthesis of TNFα was not significantly modified by any TKI. 6) MDMs acquired a rounded morphology with dasatinib, but synthesis of mitochondrial ATP and adhesion capacity did not change.
**Conclusion:** Dasatinib reverted SAMHD1 phosphorylation of MDMs and induce protection from HIV-1 infection, being imatinib less effective. Dasatinib, but not imatinib, interfered with IFNγ production, which has been involved in HIV-1 chronic inflammation. Dasatinib was more effective to inhibit HIV-infection in MDMs from healthy donors but the interference with IFNγ synthesis was more effective in MDMs from HIV-infected individuals.

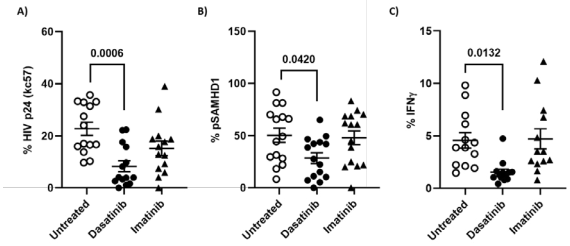



**Figure 1.** Synthesis of viral proteins (p24) (**A**), SAMHD1 phosphorylation (**B**), and LPS-induced IFNγ production (**C**) from MDMs of HIV-infected individuals treated with dasatinib or imatinib before infection with JR_FL_renilla for 48h.

## 346 CRISPR-Cas9–MEDIATED EXONIC DISRUPTION DELIVERED BY LNP FOR HIV-1 ELIMINATION

New Investigator Scholar

**Mahmudul Hasan**[1], Jonathan Herskovitz[1], Milankumar Patel[1], Farah Shahjin[1], Bhavesh D. Kevadiya[1], Howard E. Gendelman[1]

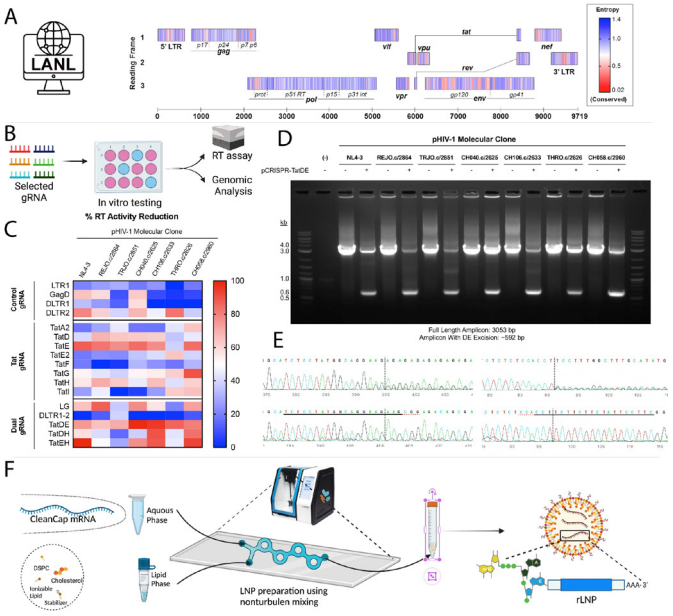
[1]*University of Nebraska Medical Center, Omaha, NE, USA*

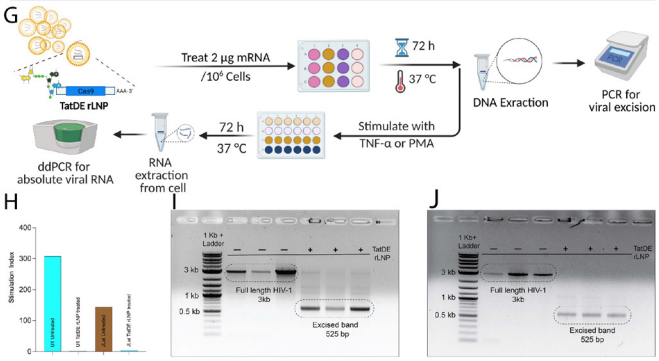
**Background:** A barrier to HIV-1 cure rests in the persistence of proviral DNA in infected CD4+ leukocytes. The high HIV-1 mutation rate leads to viral diversity, immune evasion, and consequent antiretroviral drug resistance. While CRISPR-spCas9 can eliminate latent proviral DNA, its efficacy is limited by HIV strain diversity and precision target cell delivery.

**Methods:** A library of guide RNAs (gRNAs) designed to disrupt five HIV-1 exons (tat1-2/rev1-2/gp41) was constructed. The gRNAs were designed against a consensus sequence of the transcriptional regulator tat from 4004 curated HIV-1 strains. Efficacy of the gRNAs were affirmed by cell entry through transfection, electroporation, or by lentivirus or lipid nanoparticle (LNP) delivery. Treated cells were evaluated for viral excision by monitoring HIV-1 DNA, RNA, protein, and progeny virus levels.

**Results:** Virus production was reduced in all transmitter founder strains by 82 and 94% after CRISPR TatDE transfection or lentiviral transduction treatments, respectively. No recorded off-target cleavages were detected. Electroporation of TatDE ribonucleoprotein and delivery of LNP TatDE gRNA and spCas9 mRNA to latently infected cells resulted in up to 100% viral excision. Protection against HIV-1-challenge or induction of virus during latent infection, in primary or transformed CD4+ T cells or monocytes, was achieved. We propose that multi-exon gRNA TatDE disruption delivered by LNPs enables translation for animal and human testing.

**Conclusion:** These results provide "proof of concept' for CRISPR gRNA treatments for HIV-1 elimination. The absence of full-length viral DNA by LNP delivery paired with undetectable off-target affirms the importance of payload delivery for effective viral gene editing.




## 347 BRAIN PENETRANT CSF1R INHIBITOR REDUCES BRAIN VIRUS BURDEN IN SIV-INFECTED MACAQUES

**Laurent D. Zablocki-Thomas**[1], Evan S. Leung[2], Jinbum K. Dupont[3], Julian B. Hattler[2], Diana G. Bohannon[2], Jolanta Kowalewska[2], Marcelo J. Kuroda[1], Woong-Ki Kim[2]

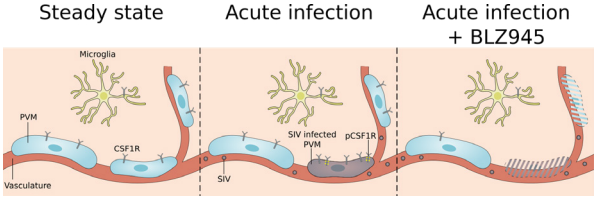
[1]*University of California Davis, Davis, CA, USA,* [2]*Eastern Virginia Medical School, Norfolk, VA, USA,* [3]*Uniformed Services Medical School, Bethesda, MD, USA*

**Background:** Perivascular macrophages (PVMs) and, to a lesser degree, microglia are targets and reservoirs of HIV and SIV in the brain, hindering viral clearance despite antiretroviral therapy. Previously, we demonstrated that colony-stimulating factor 1 receptor (CSF1R) in PVMs was upregulated and activated in simian immunodeficiency virus (SIV)-infected rhesus macaques with encephalitis, correlating with SIV infection of PVMs. Herein, we investigated the role of the CSF1R in the brain during acute infection using BLZ945, a highly selective brain penetrant CSF1R kinase inhibitor.

**Methods:** A total of 9 Indian rhesus macaques were infected with SIVmac251 and depleted of CD8 cells with anti-CD8 antibody administered on days 6, 8 and 12 post infection. Six animals received a daily oral dose of either 10 or 30 mg/kg of BLZ945 (each with n=3), starting on days 10 post infection, for 20-30 consecutive days until euthanasia. We monitored plasma and cerebrospinal fluid (CSF) viral load by qRT-PCR. In brain tissue collected postmortem, we counted immunohistochemistry-stained macrophages (CD206+ or CD163+) and microglia (P2RY12+) by microscopy and also measured tissue viral DNA (vDNA) load by qPCR. An untreated control group includes the remaining 3 acutely infected.

**Results:** With the high-dose BLZ945 treatment, there was a significant reduction in cells expressing CD163 and CD206 across all 3 brain areas examined, compared to low-dose treatment and control groups. In 9 out of 11 tested regions, tissue vDNA load was significantly reduced with at least one of the two doses by 95 to 99%, and in some instances, even to undetectable levels. Decreased numbers of CD163+ and CD206+ cells were significantly correlated with lower levels of vDNA in all 3 corresponding brain areas. In contrast, BLZ945 treatment did not significantly affect the number of microglia. BLZ945 had no impact on plasma or CSF viral load. Serum levels of two major liver enzymes, alanine transaminase and aspartate transaminase were not significantly elevated, and liver histopathological examinations showed no sign of drug-induced injury with BLZ945 treatments. No notable differences exist in term of blood leukocyte populations between the groups.

**Conclusion:** Our results indicate that doses as low as 10 mg/kg of BLZ945 are sufficient to reduce the tissue vDNA load in the brain with no appeared adverse effect. This study provides evidence that infected PVM are highly sensitive to CSF1R inhibition, opening new possibilities to achieve viral clearance.



## 348 COMBINATION OF PD-1 BLOCKADE AND AZD5582 THERAPY IN SIV+ MONKEYS

New Investigator Scholar

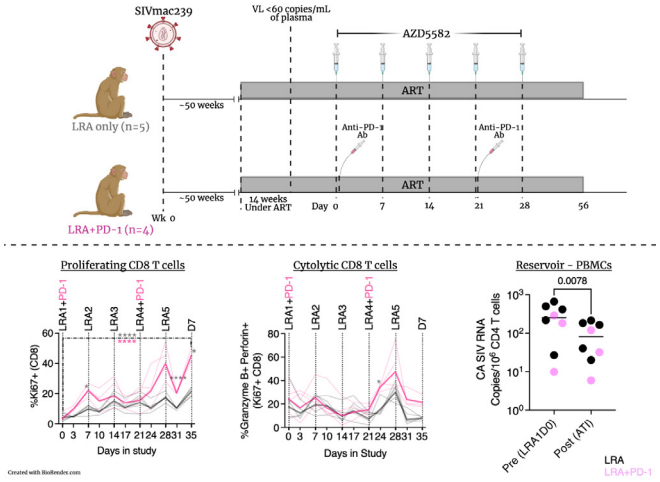
**Bhrugu Yagnik**[1], Sheikh A. Rahman[1], Gordon J. Freeman[2], Rafi Ahmed[3], Rama R. Amara[1]
*[1]Yerkes National Primate Research Center, Atlanta, GA, USA, [2]Harvard Medical School, Boston, MA, USA, [3]Emory Vaccine Center, Atlanta, GA, USA*

**Background:** Latency reversal and restoring T cell function are the two major barriers to HIV cure and there is a need for the development of therapeutic strategies that both reverse latency and restore T and B cell function to facilitate immune mediated clearance of the reactivated latent CD4 T cells. PD-1 blockade has not only been shown to potentiate HIV/SIV latency reversal but also to reverse immune exhaustion, improve antiviral immunity and reduce viral reservoirs. Therefore, the objective of this study was to combine PD-1 blockade with AZD5582 (a potent latency reversal agent, LRA) as a "shock and kill" approach and study safety, virological and immunological effects in SIV infected and ART suppressed rhesus macaques (RMs).

**Methods:** A total of 9 RMs were chronically infected with SIVmac239 for 2 years and were on a second cycle of daily ART for 14 weeks with complete viral suppression. Both the groups received five weekly infusions of AZD5582 (0.1mg/kg), one without (LRA only, n=5) and the other with two primatized anti-PD-1 antibody (10mg/kg) infusions at 1st and 4th cycle of AZD5582 infusion (LRA+PD-1, n=4) under ART. Plasma viral load and immunophenotypic analyses on PBMCs, lymph nodes and gut were performed throughout the study. RNA-Seq analyses were performed at days 0, 3 and 7 post 1st infusion. Cell Associated DNA and RNA were measured pre- and post-treatment in PBMCs.

**Results:** Strong latency reversal as well as instances of sustained viremia were observed in both the groups with no significant difference in events of viral rebound between the groups. Interestingly, flow cytometry data revealed that combination of PD-1 blockade and AZD5582 but not AZD5582 alone, showed a robust increase in proliferating total and memory CD4 and CD8 T cells with each AZD5582 administration in PBMCs. Total CD8 T cells co-expressing granzyme B and perforin (cytolytic potential) also significantly increased following the 2nd infusion of anti-PD-1 antibody. The combination group also showed an increase for T regs. Similar immune changes were observed in LN and Gut. Treatment with AZD5582 decreased cell associated RNA copies in PBMCs and addition of PD-1 blockade didn't reduce it further.

**Conclusion:** In summary, combined treatment of PD-1 blockade and AZD5582 is safe and effective in inducing latency reversal. Despite no additive advantage on reservoir size, the combined treatment changed the landscape of T cell responses in blood and tissues.




## 349 VIRAL AND BIOMARKER OUTCOMES OF AN ENGINEERED bNAb IN ART-SUPPRESSED PARTICIPANTS

**Yanhui** Cai[1], Lisa Selzer, Peter J. Ruane, Eric S. Daar[3], Princy N. Kumar[4], Laurie VanderVeen[1], Liao Zhang[1], Jeffrey Wallin[1], Devi SenGupta[1], Sean E. Collins[1], Kimberly Workowski[5], Joseph J. Eron[6], Edwin DeJesus[7]
*[1]Gilead Sciences, Inc, Foster City, CA, USA, [2]Ruane Clinical Research Group, Inc, Los Angeles, CA, USA, [3]Harbor–UCLA Medical Center, Torrance, CA, USA, [4]MedStar Health, Washington, DC, USA, [5]Emory University, Atlanta, GA, USA, [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [7]Orlando Immunology Center, Orlando, FL, USA*

**Background:** Broadly neutralizing antibodies (bNAb) against HIV-1 may target and eliminate virally infected cells expressing envelope (Env) protein, potentially reducing HIV-1 reservoir in people with HIV (PWH). Increased HIV-specific T cell responses have been observed in PWH receiving bNAb therapy during antiretroviral therapy (ART) interuption. We evaluated viral reservoirs and HIV-specific T cell responses in ART-suppressed participants receiving the bNAb elipovimab (EVM), an engineered variant of PGT121 with enhanced Fc-gamma receptor binding.

**Methods:** This Phase Ib single and multiple ascending dose study enrolled 32 virologically suppressed PWH on ART and randomized them 3:1 to receive intravenous EVM or placebo with follow-up through day 169 (Cohorts 1 and 2) or 225 (Cohorts 3 and 4). Cohorts 1 (150mg) and 2 (500mg) received a single dose of EVM; Cohorts 3 (150mg) and 4 (500mg) received 5 doses administered biweekly. Plasma and PBMCs were collected longitudinally. HIV-specific T cell responses were evaluated with IFN-γ ELISpot assay ex vivo using PBMCs stimulated with Clade B HIV-1 consensus peptides (Gag, Env, Nef and Pol). Total HIV DNA and intact HIV proviral DNA (IPDA) were assessed at baseline and after dosing. EVM sensitivity at baseline was defined using published Env signature. Proviral genotypes were determined using GenoSure HIV Envelope RNA Assay.

**Results:** Modest increase in HIV-specific T cell responses were observed 12 weeks after the last dose of EVM in the participants of cohort 4, which returned to baseline 24 weeks later. The highest fold increase (FI) was Pol-specific T cells [median FI=2.4; interquartile range (IQR) 1.7 to 3.6] followed by Env-specific T cells (median FI=1.9, IQR 0.9 to 5.8). No significant change in HIV-specific T cells were observed in the other 3 cohorts. Overall, 7/31 (23%) participants were sensitive to EVM by genotyping; 3/6 who received multiple doses of EVM 500mg in cohort 4 were sensitive by genotyping, including 2 participants with the highest FI in HIV-specific T cells. No significant difference in total HIV DNA or IPDA were detected following treatment in any cohort (Wilcoxon matched-pair rank test).

**Conclusion:** EVM may engage the immune system and augment HIV-specific T cell response in PWH harboring bNAb sensitive viruses. Whether bNAbs can facilitate clearance of the replication competant latent HIV reservoir remains an area of interest and would likely require combinations of bNAbs to increase the breadth of coverage of diverse viruses.

## 350 DNA-eCD4-Ig DECREASED HIV-1 RESERVOIR ON ART-DELAYED VIRAL REBOUND IN HUMANIZED MICE

New Investigator Scholar

**Zhe Yuan**[1], Mansi Purwar[1], Opeyemi S. Adeniji[1], Ziyang Xu[2], Colin Hart[1], Kwasi Gyampoh[1], Guorui Zu[1], Abhijeet J. Kulkarni[1], Mohamed Abdel-Mohsen[1], David Weiner[1], Luis J. Montaner[1]
*[1]Wistar Institute, Philadelphia, PA, USA, [2]University of Pennsylvania, Philadelphia, PA, USA*

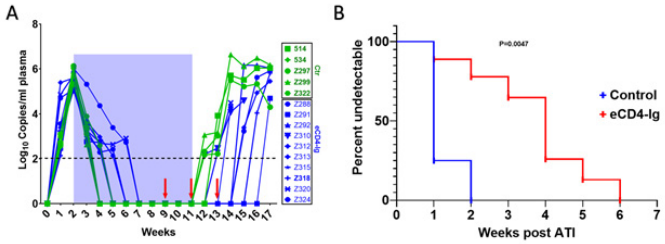
**Background:** AAV-delivered eCD4-Ig can prevent infection with more breath than broadly neutralizing antibodies (bNAbs) and is able to block multiple challenges of SHIV in NHP and HIV in hu-mice models. However, the use of eCD4-Ig on affecting HIV levels on ART or during ART interruption have not been studied. DNA Launched (DL) eCD4-Ig with co-delivery of enzyme IgE-TPST2 in vivo leads to expression of this highly structured molecule with enhanced sulfation, which is functional and neutralizes the HIV-1 Global Panel with high potency. In this study, we tested DL-eCD4-Ig co-delivered with IgE-TPST2 in HIV-infected bone marrow-liver-thymus (BLT) humanized mice under ART suppression and after ART interruption.

**Methods:** AAV delivered human cytokine-differentiated BLT hu-mice were infected with transmitted/ founder (T/F) virus HIVsuma. Following 4 to 5 weeks of viremia and subsequent suppression on cART (FTC+TDF+RAL), DL-eCD4-Ig was delivered IM three times over two experiments totaling 17 treated and 12 controls. In-vivo expression of DL-eCD4-Ig was detected by ELISA and dosing optimized. Leukocyte subsets and activation were measured by flow cytometry. Plasma viral load (sensitivity >200 copies/ml), CD4+T cells and NK cells were monitored weekly. Proviral DNA size was measured by total HIV DNA assay. Differences between and within groups were determined by two-sided nonparametric tests with 0.05 alpha. Survival analysis used to evaluate time of viral rebound between groups.

**Results:** We confirmed hu-mice plasma with addition of eCD4-Ig can elicit strong ADCC effect against HIV-1 infected cells. DL-eCD4-Ig treatments on ART

maintained suppression and resulted in a significant delay of the viral rebound after ART interruption with a retention of weight and CD4 T-cell frequency. Temporal mean 12.5% CD4+ T cells decline and mean 5-fold increase in NK% in CD45+ cells were observed 1 week after the electroporation on ART without any detectable viral load. Total HIV proviral DNA in PBMC showed a significant decrease (p=0.497) following first dose of eCD4-Ig on ART consistent with delay in viral rebound.

**Conclusion:** DNA Launched eCD4-Ig co delivered with IgE-TPST2 administered to hu-mice on ART was able to reduce the cellular levels of HIV-1 and delay viral rebound after ART interruption indicating eCD4-Ig could be pursued as a strategy to achieve a cure or ART-free remission of HIV infection.




## 351 EFFICACY OF Ad26/MVA + Env + VESATOLIMOD THERAPEUTIC VACCINATION IN RHESUS MACAQUES

**John D. Ventura**[1], Joseph P. Nkolola[1], Abishek Chandrashekar[1], Erica N. Borducchi[1], Jinyan Liu[1], David L. Hope[1], Victoria M. Giffin[1], Katherine McMahan[1], Romas Geleziunas[2], Jeffrey Murry[2], Mark G. Lewis[3], Maria G. Pau[4], Merlin Robb[5], Dan Barouch[1]

*[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]Gilead Sciences, Inc, Foster City, CA, USA, [3]BIOQUAL, Inc, Rockville, MD, USA, [4]Janssen Infectious Diseases–Diagnostics BVBA, Beerse, Belgium, [5]Walter Reed National Military Medical Center, Bethesda, MD, USA*

**Background:** Recent work assessing the immunogenicity and efficacy of therapeutic vaccination in SIV/SHIV infected rhesus macaques while on antiretroviral therapy (ART) has shown promise. We asked whether modifying a current adenovirus serotype 26 (Ad26) and modified vaccinia Ankara (MVA) therapeutic prime boost regimen expressing SIV Gag, Pol, and Env, in combination with the TLR7 agonist vesatolimod and an additional SIV gp140 subunit (i.e. SIV Env) with alum adjuvant boost, would enhance overall anti-SIV cellular immunity, reduce viral reservoirs, facilitate a delay in viral rebound, and induce virologic control following ART interruption (ATI) in ART-suppressed rhesus macaques.

**Methods:** SIV-specific cellular immune responses post Ad26/MVA + Env with repeated Vesatolimod administration between each Env boost were determined via ELISpot and intracellular cytokine secretion assays. Humoral responses were assessed by SIV Env-specific IgG ELISA. Intact replication-competent proviruses were measured with a digital droplet PCR-based intact proviral DNA assay (IPDA) with SIV-specific primer sets. Vesatolimod efficacy was determined with serum cytokine profiling and expression of peripheral activation markers (i.e. CD69) using multiparameter flow cytometry. Therapeutic efficacy of the vaccine regimen was assessed longitudinally up to 198 days following ART interruption by measuring plasma viral loads via qRT-PCR.

**Results:** Ad26/MVA vaccination with vesatolimod was highly immunogenic, and animals receiving the SIV Env boost with alum adjuvant exhibited enhanced Env-specific antibody and T cell responses. Virologic control was observed in 5/12 animals that received the Ad26/MVA regimen and in 5/12 animals that received the Ad26/MVA + Env regimen, both in combination with vesatolimod. No appreciable difference in time to rebound was observed between treatment groups. SIV-specific cellular immune responses correlated strongly with virologic control post ATI.

**Conclusion:** The data from this study showed that Ad26/MVA + SIV Env with alum adjuvant therapeutic vaccination and vesatolimod administration led to enhanced SIV-specific cellular immune responses when compared to the Ad26/MVA regimen alone. Notably, the number of animals exhibiting post-rebound virologic control was similar between both treatment groups. These results provide a rationale for future studies involving Ad26/MVA therapeutic vaccine regimens as a potential HIV-1 functional cure.

## 352 BEAT2: PEG-IFN-A2B + 3BNC117 AND 10-1074 KEEPS HIV AT <20 C/ML DURING 26 WEEK ATI

**Pablo Tebas**[1], Livio Azzoni[2], Emmanouil Papasavvas[2], Grace Choi[1], Susan S. Ellenberg[3], Marina Caskey[4], Bonnie Howell[5], Daria Hazuda[5], Christos Petropoulos[6], Kenneth Lynn[3], Linden Lalley-Chareczko[7], Jay R. Kostman[7], William R. Short[1], Karam Mounzer[7], Luis J. Montaner[2]

*[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Wistar Institute, Philadelphia, PA, USA, [3]Hospital of the University of Pennsylvania, Philadelphia, PA, USA, [4]The Rockefeller University, New York, NY, USA, [5]Merck & Co, Inc, West Point, PA, USA, [6]Monogram BioSciences, San Francisco, CA, USA, [7]Philadelphia FIGHT, Philadelphia, PA, USA*

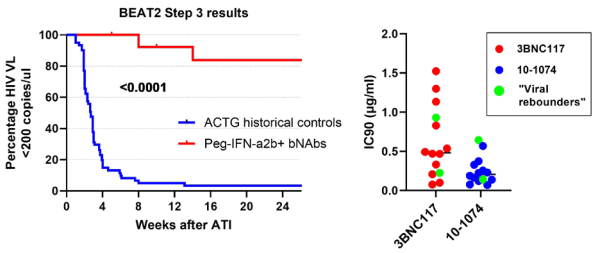
**Background:** Broadly neutralizing anti-HIV monoclonal antibodies (bNAbs) have shown promising results for the prevention and treatment of HIV. We present the results of Step 3 of BEAT2 evaluating whether the combination of bNAbs 3BNC117 and 10-1074 plus peg-IFN-α2b can prevent or delay the return of viremia during 26 weeks of ART interruption (ATI).

**Methods:** BEAT2 (NCT03588715) is an open-label study of the safety, tolerability and innate immune mechanisms activation of combining peg-IFN-α2b with two broadly neutralizing antibodies (3BNC117 and 10-1074) in the setting of well controlled chronic HIV infection and an ATI. Participants had bNAb sensitive virus using the Monogram DNA assay ($IC_{90}$ < 2.0 µg/mL (3BNC117) and <1.5 µg/mL (10-1074)). Participants received 30 weekly doses of peg-IFN-α2b (1.5µg/kg) starting at step 2 (4 weeks on ART) and continued at step 3 (26 weeks of ATI), and seven paired IV injections of the bNAbs (30 mg/kg of each) at weeks 0, 2, 4, 8, 12, 16, 20 of step 3. Step 3 ended one week after last dose of peg-IFN-α2b. ART restart criteria: 6 weekly measurements > 1,000 copies/ml. Viral rebound: confirmed HIV-1 RNA of ≥200 c/ml.

**Results:** We enrolled 14 participants: 12 males, 11 African American, median CD4 count was 869 c/mm3 (IQR 739-1079) and nadir CD4 >200 c/mm3. 79% were on INSTI and 14% on PI regimens at entry. The combination immunotherapy was safe and well tolerated. 3 participants experienced infusion reactions during the administration of 3BNC117 (chills), 2 of them withdrew consent due to infusion chills during the intervention with undetectable HIV-1 RNA (at w5 and w10 of step 3). Two participants had viral rebound 2/14 (14%) (w8 and w14) during immunotherapy with 10/14 completing 26 weeks of step 3. No grade > 3 related AEs were observed. Participants maintained suppression during the ATI when compared to non-NNRTI historical chronically infected controls from prior ACTG studies (n=61) (Logrank Mantel-Cox p<0.0001; HR (logrank) 16.7 95%CI 9.9-27-9) (Figure).

**Conclusion:** Passive administration of a combination of bNAbs plus peg-IFN-α2b in subjects with susceptible virus maintains viral suppression for 26 weeks in the absence of traditional ART in most participants. We are currently evaluating step 3 effects on the HIV reservoir, as well as pharmacokinetics, immunological and virological parameters. These data will inform the next strategies to utilize bNAbs and interferon, alone or in combination in cure related strategies.

Figure: Left: Proportion of participants with confirmed HIV-1 RNA ⩾200 copies/ml. Right: Baseline Phenosense mAb susceptibilities. In green, the two "rebounders".




## 353 AC MIMETICS REACTIVATE HIV AND REDUCE THE VIRAL RESERVOIR IN HUMANIZED MICE

**Jaspreet Jain**[1], Tram N. Pham[1], Nicolas Bellini[1], Frédéric Dallaire[1], Thomas T. Murooka[2], Rémi Fromentin[3], Nicolas Chomont[3], Eric A. Cohen[1]

*[1]Montreal Clinical Research Institute, Montreal, Canada, [2]University of Manitoba, Winnipeg, Canada, [3]Centre de Recherche du CHUM, Montreal, Canada*

**Background:** Antiretroviral therapy (ART) suppresses HIV replication without eliminating viral reservoirs (VR). VR cells express high levels of Inhibitors of Apoptosis Proteins (IAPs), enabling their prolonged survival. PKC agonists, the

most potent HIV latency reversing agents (LRA), reactivate VR via activation of canonical NFκB pathway, without VR elimination. However, since they are likely to greatly increase inflammation in vivo, they are difficult to evaluate clinically. Thus, there is a need for novel therapeutic interventions. Herein, SMAC mimetics (SM), targeting the non-canonical (nc)-NFκB pathway, were studied in humanized (hu) mice as novel LRA to preferentially induce apoptosis of HIV-infected cells.
**Methods:** We first studied the effect of SM on CD4+ T-cell models of HIV latency and HIV-CRMZ dual reporter virus infected primary CD4+ T-cells (E2-Crimson under the HIV LTR and ZS-Green under the EF1α promoter). In vivo toxicity of SM was assessed in hu-BLT mice. SM dependent reduction of infected cells was determined ex vivo using cells isolated from bone-marrow and spleen of HIV-infected hu-mice. Thereafter, SM effect on HIV reactivation and reservoir reduction was documented in vivo in virally-suppressed hu-mice. Finally, the effect of SM was assessed on the magnitude of viral rebound following ATI.
**Results:** We tested a panel of commercially available SM as LRA and obtained HIV reactivation in upto 50% of latently infected cells using bivalent SM via nc-NFκB pathway activation. SM mediated reactivation and apoptosis of latently infected cells was observed to be dependent on IAPs degradation. Next, using HIV-CRMZ viral construct, we show that SM preferentially eliminate HIV-productively and latently infected primary CD4+ T cells. SM-mediated reduction of infected T- and myeloid cells was confirmed ex vivo in cells from infected hu-mice. We further document that SM reactivate HIV in ART-supressed infected hu-mice, as shown by increased plasma viremia and higher cell-associated (ca) HIV-RNA. We report, for the first time, SM-mediated reduction in ca total and integrated HIV-DNA in the lymphoid and non-lymphoid tissues. Moreover, SM-treated mice exhibited reduced viremia (10-100-fold), less HIV-infected CD4+ T cells and lower total and integrated HIV-DNA following ATI.
**Conclusion:** We show that SM reactivate HIV and, by inducing infected cell apoptosis, can potentially reduce the VR. SM are potential new HIV LRAs that, combined with ART, results in partial control of viral replication upon ATI.

## 354 INDUCIBLE RESERVOIR IN TISSUES, BUT NOT IN PERIPHERY, PREDICTS FUNCTIONAL CURE OF SIV

New Investigator Scholar

**Adam J. Kleinman**[1], Sindhuja Sivanandham[1], Ranjit Sivanandham[1], Paola Sette[1], Benjamin B. Policicchio[1], Cuiling Xu[1], Quentin Le Hingrat[1], Egidio Brocca-Cofano[1], Dongzhu Ma[1], Ivona Pandrea[1], Cristian Apetrei[1]
[1]*University of Pittsburgh, Pittsburgh, PA, USA*

**Background:** HIV persistence in reservoirs requires lifelong antiretroviral therapy (ART), calling for cure. Latency reversing agents (LRAs), such as the histone deacetylase inhibitor romidepsin, reactivate and clear HIV/SIV through cell-mediated immune responses and viral lytic effects ("shock and kill").
**Methods:** We tested a total of four single infusions and two "double infusions" (two infusions separated by 48 hours) of romidepsin (7 mg/m2) in five rhesus macaques (RM) infected with SIVsab, our model of SIV functional cure that does not require ART for viral control. Two animals received CD8-depleting antibody after the third RMD infusion instead of moving to double infusions.
**Results:** Off ART, romidepsin reactivated SIV in all RMs. Subsequent RMD infusions diminished reactivation and some infusions did not yield detectable reactivation. Specifically, two animals did not reactivate after the second and third rounds, while two other animals presented with no detectable viremia after the fifth and sixth rounds of RMD. Double infusions were given to the RMD-reactive animals after the third round of single infusions and was well tolerated, induced immune activation, and effectively reactivated SIV. Minimal changes in the levels of cell-associated viral DNA occurred, but viral outgrowth from CD4+ cells was decreased in the RMs lacking reactivation after receiving a CD8+-depleting antibody (RM89), and after the fifth romidepsin treatment (RM94). The frequency of SIV-specific CD8+ T cells increased after longitudinal romidepsin infusions, mirroring lack of reactivation.
**Conclusion:** Sequential decreases in viral reactivation with repeated romidepsin administrations and absence of viral reactivation after CD8+ T-cell depletion suggest that, in the context of healthy immune responses, romidepsin decreased the inducible viral reservoir, and that repeated LRA administrations and viral reactivations induced greater immune-mediated viral control, suggesting that improving immune function should be the start point of HIV cure strategies.

## 355 EFFECT OF HIGH-DOSE VITAMIN D3 ON THE HIV RESERVOIR: A RANDOMIZED CONTROLLED TRIAL

**Matthew C. Pitman**[1], Niamh Meagher[1], David J. Price[1], Ajantha Rhodes[1], Judy Chang[1], Barbara Scher[1], Brent Allan[2], Alan Street[3], James McMahon[4], Thomas A. Rasmussen[1], Paul U. Cameron[1], Jennifer Hoy[4], Stephen J. Kent[5], Sharon Lewin[1]
[1]*Doherty Institute for Infection and Immunity, Melbourne, Australia,* [2]*Living Positive Victoria, Melbourne, Australia,* [3]*Royal Melbourne Hospital, Melbourne, Australia,* [4]*Alfred Hospital, Melbourne, Australia,* [5]*Melbourne Sexual Health Centre, Melbourne, Australia*

**Background:** Chronic inflammation may contribute to HIV persistence on antiretroviral therapy (ART) through proliferation of infected CD4+ T cells and/or exhaustion of an effective immune response against HIV. Vitamin D3 has been shown to inhibit T cell proliferation and exhaustion in vivo. We sought to determine whether vitamin D3 could inhibit HIV persistence and immune cell activation, differentiation and exhaustion on ART.
**Methods:** In this pilot randomized double-blind placebo-controlled trial, we enrolled participants aged over 18 years living with HIV-1 on ART with plasma HIV RNA < 40 copies/ml for at least 3 years. Participants were randomized to take 10,000 international units vitamin D3 or placebo orally daily for 24 weeks and were followed for a further 12 weeks. The primary outcome was the difference between arms in the mean change in frequency of total HIV DNA within CD4+ T cells from baseline to week 24. Virology was evaluated with mixed effects negative binomial regression models while immunology and 25-hydroxyvitamin D levels were evaluated using mixed effects linear models.
**Results:** Thirty participants (all cisgender male) were enrolled with 15 assigned to each intervention. There was a 1.15 (95% confidence interval (CI) 0.94 – 1.40) fold difference in the vitamin D3 arm compared to the placebo arm in change in frequency of total HIV DNA from week 0 to week 24 (p = 0.19). However, there was a 1.24 (95% CI 1.01 – 1.51) fold increase (p = 0.039) from week 0 to week 12 and a 0.76 (95% CI 0.62 – 0.94) fold decrease (p = 0.009) from week 0 to week 36 in frequency of total HIV DNA relative to placebo. Decreases in frequencies of effector memory and terminally differentiated CD4+ T cells and increases in frequencies of activated and exhausted CD8+ T cells and activated NK cells were also seen compared to placebo. 25-hydroxyvitamin D levels remained elevated at week 36 relative to placebo.
**Conclusion:** Frequency of total HIV DNA was not affected by vitamin D3 at week 24 but decreased at week 36 relative to placebo. This could relate to antiproliferative effects of vitamin D3 over time, reducing frequency of more differentiated CD4+ T cell subsets enriched for HIV DNA, and/or to unexpected increases in CD8+ T cell and NK cell activation. Persistently elevated 25-hydroxyvitamin D levels at week 36 likely reflect its long half-life. Larger studies are now required potentially including ART interruption to determine whether vitamin D3 can exert a clinically significant impact on the HIV reservoir.

## 356 CARD8 SENSITIZATION THROUGH DPP9 INHIBITION ENHANCES KILLING OF HIV-INFECTED CELLS

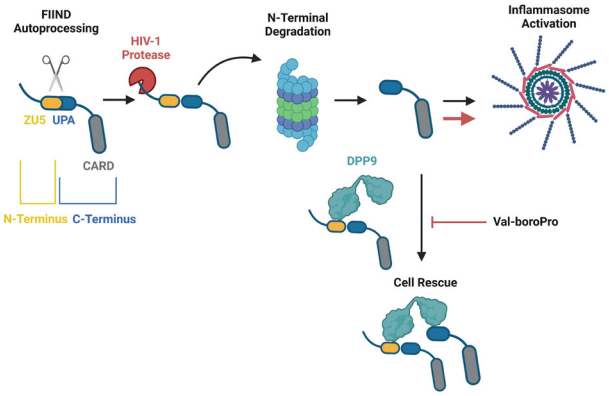
New Investigator Scholar

**Kolin Clark**[1], Qiankun Wang[1], Josh Kim[1], Liang Shan[1]
[1]*Washington University in St Louis, St Louis, MO, USA*

**Background:** The inflammasome sensor CARD8 can sense intracellular HIV-1 protease activity which leads to targeted cell killing of HIV-1 infected cells. This premature intracellular activation can be achieved using NNRTIs. However, high concentrations of NNRTIs are required for sufficient CARD8 sensing. This calls for the elucidation of ways to sensitize the CARD8 inflammasome. One way in which this can be achieved is through inhibition of the CARD8 negative regulator DPP9. The DPP9 chemical inhibitor Val-boroPro (VbP) can activate the CARD8 inflammasome in CD4+ T cells and was tested for its ability to enhance CARD8 inflammasome sensing of HIV.
**Methods:** CD4+ T cells were isolated from PBMC of healthy donors, infected with a pNL4-3-GFP reporter virus, and treated with NNRTIs with or without VbP. Functional validation was tested through knocking out key CARD8 inflammasome components with CRISPR/Cas9 in THP-1 cells. Site-directed mutagenesis via PCR was used to introduce NNRTI resistance associated mutations into pNL4-3-GFP. To test the combination strategy in vivo we treated humanized mice that were transfused with infected, primary CD4+ T Cells. We collected blood and tissues 24 hours post-injection and assayed for killing efficacy via flow cytometry.
**Results:** High micromolar concentrations are needed for efficient killing of HIV-1 infected cells in vitro. This efficacy is further diminished by the presence

of human serum due to NNRTIs' high binding affinity. Treatment of HIV infected cells with VbP in combination with NNRTIs enhances killing. This relationship is synergistic and dependent upon the CARD8 inflammasome. VbP alone was also found to induce targeted killing of infected cells. Combination treatment was able to restore NNRTI efficacy in the presence of human serum and can partially overcome NNRTI resistance. We also show that monotherapy of NNRTIs (34% killing) or VBP (30%) can kill HIV-1 infected cells in humanized mice which is greatly enhanced when using a combination treatment (68%).

**Conclusion:** DPP9 inhibition can sensitize the CARD8 inflammasome which ameliorates potential barriers to NNRTI efficacy. We show that this combination strategy is an effective treatment for the in vivo elimination of HIV-1 infected cells in humanized mice. This work offers promise for utilizing the CARD8 inflammasome pathway for an HIV cure strategy. We also highlight that DPP9 inhibition can induce killing of HIV infected cells, which provides an alternative target for HIV cure drug development.




## 357 HIV-1 VIRAL RESERVOIR DISRUPTION WITH PANOBINOSTAT AND IFN-A

New Investigator Scholar

**Marie Armani-Tourret**[1], Ciputra A. Hartana[1], Yelizaveta Rassadkina[1], Ce Gao[1], Katrina Shea[2], Amy Sbrolla[2], Xu Yu[1], Rajesh T. Gandhi[2], Daniel Kuritzkes[3], Mathias Lichterfeld[1]

*[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Brigham and Women's Hospital, Boston, MA, USA*

**Background:** Current antiretroviral therapies (ART) are unable to eradicate HIV-1, mainly because the virus persists in latently infected cells that can fuel viral rebound after treatment interruption. Pharmacological reactivation of viral transcription may sensitize viral reservoir cells to immune-mediated killing and reduce the long-term persistence of virus-infected CD4+ T cells. The ACTIVATE study is a prospective, randomized clinical trial in which the histone deacetylase inhibitor panobinostat is administered as a latency-reversing agent in combination with pegylated IFN-α2a as an innate immune modulator to reduce the viral reservoir.

**Methods:** To assess the impact of panobinostat and IFN-a2a on HIV reservoirs, ART-treated participants were randomized to receive panobinostat alone (n=4), the combination of panobinostat and pegIFN-a2a (n=9) or pegIFN-a2a alone (n=4). Proviral HIV-1 DNA was analyzed using the intact proviral DNA assay (IPDA); CD4 T cell-associated HIV-1 RNA was quantified by RT-ddPCR assay. H3 acetylation and innate and adaptive cellular immune responses were analyzed by flow cytometry.

**Results:** After 4 days of treatment with panobinostat alone or in combination, the proportion of acetylated histone H3-expressing CD4T cells increased by 6.3-fold (MFI increase of 2.6, p<0.0005). In parallel, a significant increase of long-LTR transcripts was observed (fold increase 2.26, p=0.0078) which reflects an increase in viral transcription. However, no significant increases were noted for more elongated HIV-1 RNA transcripts. Proportions of CD4+ and CD8+ T cells expressing granzyme A, granzyme B and perforin as well as the Th1 transcription factor Tbet increased during combined treatment. The expression of co-stimulatory molecules (CD40, CD86, CD83) increased in conventional DC2 and pDCs in participants receiving pegIFN-α2a. Similarly, the frequency of activated CD38+ and NKp30+ cytotoxic NK cells (CD16+ CD56+) increased significantly at day 4 in these participants. Despite reactivation of viral transcription and activation of the immune system after treatment, no changes in HIV-1 DNA levels, determined by IPDA, were observed.

**Conclusion:** Results from ACTIVATE study indicate that the study medication induces HIV-1 transcription and augments innate and adaptive immune effector cells, without appreciably affecting HIV-1 DNA levels in our current analysis. Further studies will be conducted to evaluate possible changes in proviral positioning relative to activating epigenetic chromatin features.

## 358 IMPACT OF INFLUENZA AND PNEUMOCOCCUS VACCINES ON CELLULAR HIV RNA TRANSCRIPTION

**Sara Gianella**[1], Alan Wells1, Susanne May[2], Christy Anderson[3], Gemma Caballero[3], Laura Layman[3], Brianna Scott[3], Joseph Lonergan[1], Leticia Muttera[3], Liliana Harkness[3], Susan J. Little[3], Davey M. Smith[3]

*[1]University of California San Diego, San Diego, CA, USA, [2]University of Washington, Seattle, WA, USA, [3]University of California San Diego, La Jolla, CA, USA*

**Background:** We sought to determine if standard influenza and pneumococcus vaccines can be used to stimulate HIV reservoirs during suppressive antiretroviral therapy (ART).

**Methods:** Persons with HIV infection on suppressive ART (N=54) were enrolled in a randomized, double-blinded, placebo-controlled, cross-over trial of two clinically recommended vaccines. For three cycles, Placebo, Pneumovax®23, and Fluarix® vaccines were administered in random blinded order with a minimum 8-week wash-out period between administrations. Blood was collected at baseline and days 2, 4, 7, 14 and 30 post immunization. Levels of total cellular HIV RNA and HIV DNA were measured by droplet digital (dd)PCR. For the primary outcome, a paired-sample t-test compared differences in changes in level of CD4+ T-cell-associated HIV RNA levels from baseline to day 7 post-injection between each vaccine and placebo. We performed similar comparisons on remaining timepoints (days 2, 4, 14 and 30) and on HIV DNA levels for secondary outcomes.

**Results:** Fifty-three participants completed at least one cycle and there were no serious adverse events related to the intervention. Mean age was 45 years (standard deviation [SD]: 11); 45 (83%) were men (sex at birth) and 19 (35%) were white, 23 (43%) Hispanic and 12 (22.2%) of mixed race/ethnicity. Mean CD4+ T-cells at randomization were 753 cells/μl (SD: 249). Overall, we observed no significant differences in cellular HIV RNA transcription for either of the two vaccines compared to placebo from baseline to day 7 (Pneumovax®23 [mean difference: -999 (95%CI: -3007,1009), n=35, p=0.32] and Fluarix® [mean difference: -334 (95% CI: -1136,468), n=40, p=0.40], Figure 1 Panel A). Similarly, we did not observe significant differences in changes from baseline to days 2, 4, 14 or 30 for cellular HIV RNA levels, Figure 1 Panel B. We observed a significant transient increase in cellular HIV DNA levels when comparing changes from baseline for Pneumovax®23 to change from baseline for placebo injections at days 2 and 4 after vaccine administration (Day 2: 41 [95%CI: 4,78], p=0.03, n=33, Day 4: 78 [95%CI: 1,155], p=0.0485, n=8) but not at days 7, 14 or 30 and none for Fluarix®, Figure 1 Panels C and D.

**Conclusion:** Clinically recommended vaccines appear safe but did not stimulate the immune system strongly enough to elicit significantly noticeable cellular HIV transcription during ART.

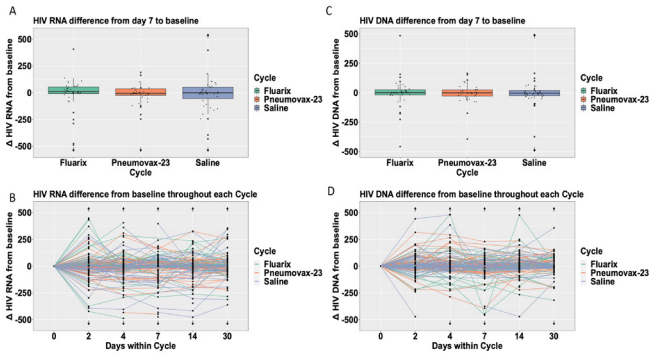



**Figure 1 Panel A/C:** Boxplot of difference in HIV RNA and DNA copies per million cells between day 7 visit and baseline. **Panel B/D:** Longitudinal Difference in HIV RNA and DNA copies per million cells at each time point compared to baseline within each cycle. Outliers > 500 | < -500 excluded; DNA (n, range): Pneumovax-23:6 (613,1554); Fluarix:1 (520); Saline:6 (-919,2930). RNA Fluarix:18 (-1228,2679); Pneumovax-23:11 (-19418,994) Saline:16 (-2224,15142). Units are DNA/RNA skGag copies per million cells.

## 359 PHASE II CLINICAL TRIAL OF VEDOLIZUMAB AND ART IN SUBJECTS WITH NO PREVIOUS ART

New Investigator Scholar

**Maria Reyes Jimenez Leon**[1], Carmen Gasca-Capote[1], Cristina Roca-Oporto[2], Nuria Espinosa-Aguilera[2], Salvador Sobrino[2], María Fontillón[2], Inmaculada Rivas-Jeremias[2], Karin Neukam[1], Jose German Sanchez-Hernandez[1], Raul

Rigo-Bonnin[3], Antonio J. Cervera[2], Rosario Mesones[2], Pompeyo Viciana[2], Luis Fernando López Cortés[2], Ezequiel Ruiz-Mateos[1]
*[1]Institute of Biomedicine of Seville, Sevilla, Spain, [2]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [3]Bellvitge University Hospital, Barcelona, Spain*

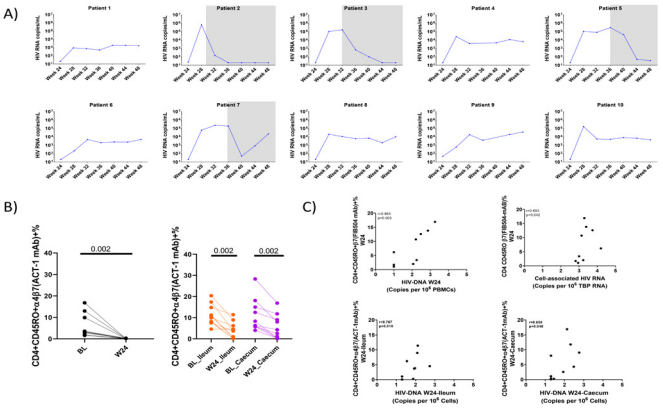
**Background:** Complete HIV remission off treatment has not been possible. The aim was to evaluate the safety and efficacy of Vedolizumab (anti-α4β7 mAb) combined with ART to achieve permanent virological remission in ART naïve subjects after ART interruption.

**Methods:** Ten patients were enrolled with CD4-T cells count of >350 cells/µl and viral load >10.000 HIV-RNA copies/ml. The time of infection was 75[40-82] days. Patients started ART together with Vedolizumab infusions(300mg) at week 0, 4, 8, 12, 16, 20 and 24 weeks. At week 24 (W24) ART and Vedolizumab treatment were interrupted. Biopsies were obtained from ileum (IL) and caecum (CC) at baseline (BL) and W24. Subjects were monitored monthly by measuring CD4+T-cell counts, viremia, Vedolizumab levels, HIV reservoir and flow cytometry to measure α4β7 levels and immune check point molecules. Criteria to restart ART were CD4 T-cells below 350 cell/µl or viral load >105 HIV-RNA copies/ml in two consecutive measurements.

**Results:** Vedolizumab was well tolerated and no adverse events occurred. No decreases in CD4+T-cell count were observed. Four patients restarted ART due to an increase of viral load (>105 HIV-RNA copies/ml). The other six patients completed the follow up with of 1590, 6250, 10000, 36450 and 4300 HIV-RNA copies/ml and no ART (Fig 1A). No differences on either time to restart ART or time to first plasma viremia of >1000 HIV-RNA copies/ml when compared to historical controls of ART interruption (n=24) were observed. Nevertheless, Vedolizumab trial group showed a viral load set point lower than the control group (p=0.008 (week40)). At W24, α4β7 was completely blocked by Vedolizumab on peripheral CD4+ T-Cells, unlike on gut (Fig 1B). We observed a decrease in HIV-DNA on PBMCs (p=0.027), IL (p=0.003) and CC (p0.008); and in cell-associated HIV RNA on PBMCs (p=0.003), IL (p=0,019) and CC (p=0,002) together with a decrease in the expression of CD4-HLA-DR (p=0.009;p=0.002), LAG3 (p=0.027;p=0.002), TIM3 (p=0.002;p=0.002), and PD1 (p=0.059;p=0.004) was observed in both tissue locations over the follow up. Reservoir was associated with the expression of CD4-α4β7(Fig 1C), PD1, TIGIT and LAG3 on PBMCs, IL and CC at W24.The decrease in cell associated HIV-RNA on PBMCs was prominent in sorted CD4+CD45RO+ β7+ cells(p=0,011).

**Conclusion:** Vedolizumab was safe and well tolerated. No dramatic virological remission after ART interruption was found in naïve subjects. Reservoir establishment in PBMCs, IL and CC was associated with α4β7 and immune check point molecules expression.

Figure_1




## 360 CARD8 ACTIVATION BY HIV-1 PR TRIGGERS GSDMD-DEPENDENT AND -INDEPENDENT CELL DEATH

New Investigator Scholar

**Qiankun Wang**[1], Liang Shan[1]
*[1]Washington University in St Louis, St Louis, MO, USA*

**Background:** Latently infected CD4+ T cells are the major barrier to HIV cure. Recently, we reported that induction of HIV-1 protease (PR) activation leads to CARD8 inflammasome-mediated pyroptosis of infected macrophages and CD4+ T cells. In macrophages, it is clear that caspase-1 (CASP1)-dependent inflammasome activation results in the cleavage and activation of gasdermin D (GSDMD), which then triggers a lytic inflammatory cell death called pyroptosis. However, GSDMD expression in lymphocytes is lower than in macrophages. It remains unclear whether CARD8 inflammasome induced killing of HIV-1-infected CD4+ T cells is GSDMD-dependent or other cell killing mechanisms are involved.

**Methods:** We treated HIV-1-infected THP-1 cells and primary CD4+ T cells with non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as rilpivirine (RPV) and efavirenz (EFV) to induce HIV PR-mediated CARD8 inflammasome activation and investigated the mechanisms of cell death in control and GSDMD-KO cells.

**Results:** We found that killing of HIV-1-infected cells by NNRTI-induced CARD8 activation was completely blocked in CASP1-KO cells. Interestingly, GSDMD knockout did not block killing of HIV-1-infected cells. When comparing the kinetics of cell death, we found that most HIV-1-infected control cells were killed by RPV within 3 hours post treatment. By contrast, cell death was not observed in infected GSDMD-KO cells in the first 6 hours and most infected GSDMD-KO cells died between 6-24 hours post RPV treatment. These results suggest that a different CASP1-dependent cell death pathway was involved in cells with insufficient or no GSDMD expression. Next, we observed that apoptotic executioner caspases-3/-7 were rapidly cleaved upon CASP1 activation.

**Conclusion:** This work reveals that HIV-1-infected cells can undergo CASP1-induced lytic cell death after CARD8 inflammasome activation in GSDMD-dependent and -independent manners. This study broadens our understanding of CARD8 inflammasome-induced cell death and has implications for the clearance of HIV-1 reservoir cells in patients.

## 361 PROLONGED VIRAL SUPPRESSION BY IMMUNOTHERAPY WITH ANTI-HIV ANTIBODIES 3BNC117/10-1074

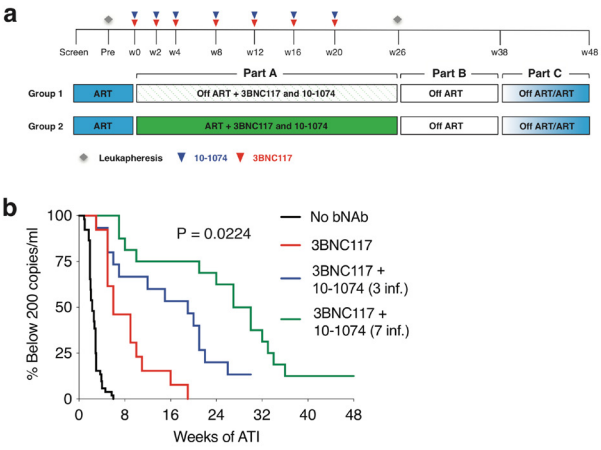
**Christian Gaebler**[1], Lilian Nogueira[1], Elina Stoffel[1], Thiago Oliveira[1], Katrina Millard[1], Martina Turroja[1], Allison Butler[1], Victor Ramos[1], Michael Seaman[2], Jacqueline D. Reeves[3], Johannes F. Scheid[4], Rajesh T. Gandhi[4], Tae-Wook Chun[5], Marina Caskey[1], Michel Nussenzweig[1]
*[1]The Rockefeller University, New York, NY, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]Abivax, Paris, France, [4]Massachusetts General Hospital, Boston, MA, USA, [5]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

**Background:** Broad and potent monoclonal anti-HIV-1 antibodies (bNabs) comprise a promising class of immunotherapeutics that have the potential to suppress HIV-1 infection, increase the rate of infected cell clearance and enhance anti-HIV immunity. However, bNabs have only been tested in short term studies and their effects on the intact latent reservoir have not been interrogated in depth. Here we report on a clinical study in which people living with HIV who started ART during chronic infection received 7 doses of a combination of two bNabs over a period of 20 weeks in the presence or absence of antiretroviral therapy (ART).

**Methods:** We conducted a Phase Ib, open label, randomized clinical trial of the combination of two bNabs, 3BNC117 and 10-1074, in the presence or absence of ART, including two study groups of people living with HIV-1 on suppressive ART for at least 12 months prior to entry (NCT03526848). Participants in Group 1 discontinued ART 2 days after the first 3BNC117 and 10-1074 infusions, while participants in Group 2 remained on ART during the period of antibody infusions through week 26 (Fig. 1a). ART was resumed according to pre-specified criteria. Participants in both groups received up to seven infusions of 30 mg/kg of each antibody over the course of 20 weeks, and were followed for a total of 48 weeks from enrollment.

**Results:** Of the 26 (23 male, 3 female) enrolled participants, 18 and 8 were randomized to Group 1 or 2, respectively. Repeated antibody infusions over the course of 20 weeks were generally safe and well-tolerated. Without pre-screening for antibody sensitivity Group 1 participants maintained viral suppression for a median of 28.5 weeks in the absence of ART which was significantly longer than after 3 infusions over 6 weeks and historical controls from non-interventional ATI studies (Fig.1b, Log-rank Mantel-Cox $P = 0.0224$ and $P < 0.0001$, respectively). Rebound viremia generally occurred after one of the two antibodies reached a concentration below 10 micrograms per milliliter and 2 of 17 participants in Group 1 that underwent ATI maintained viral suppression for at least 48 weeks (Fig. 1b).

**Conclusion:** We conclude that combination anti-HIV-1 antibody therapy can maintain viral suppression for as long as bNAb levels remain therapeutic. Furthermore, post-treatment control for 48 weeks and longer was observed in 12% of the study cohort. We are evaluating the immunomodulatory effects on the size and composition of the latent reservoir.




## 362 POST-TREATMENT CONTROLLERS LIMIT COMPLETED AND SPLICED HIV TRANSCRIPTS AFTER ATI

**Adam Wedrychowski**[1], Holly A. Martin[1], Sushama Telwatte[1], Gayatri Nikhila Kadiyala[1], Elizabeth Connick[2], Jeffrey Jacobson[3], David M. Margolis[4], Daniel J. Skiest[5], Paul Volberding[6], Frederick M. Hecht[6], Steven G. Deeks[6], Joseph K. Wong[1], Jonathan Li[7], Steven A. Yukl[1]

*[1]San Francisco VA Medical Center, San Francisco, CA, USA, [2]University of Arizona, Tucson, AZ, USA, [3]University Hospitals Cleveland Medical Center, Cleveland, OH, USA, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [5]Baystate Health, Springfield, MA, USA, [6]University of California San Francisco, San Francisco, CA, USA, [7]Harvard Medical School, Boston, MA, USA*

**Background:** The mechanisms that allow post-treatment controllers (PTC) to limit viral replication after antiretroviral therapy interruption (ATI) remain unclear. Compared to noncontrollers (NC), we hypothesized that PTC would show greater blocks to HIV transcriptional completion and splicing following ATI.

**Methods:** We measured levels of cell-associated (CA) initiated (TAR), 5'-elongated (Long), mid-elongated (Pol), completed (PolyA), and multiply-spliced (TatRev) HIV RNAs in PBMC (by RT-ddPCR) at Pre-ATI, Early-ATI, and Late-ATI time points in 11 NC and 15 PTC.

**Results:** Before ATI, PTC showed lower levels of TAR and Pol than NC (P<0.04), and a trend toward lower PolyA (P=0.052), but no difference in TatRev or HIV RNA ratios. The median viral loads (VL) at the Early-ATI visits were 143 and 6856 copies/ml for the PTC and NC, respectively (P=0.0004). From Pre-ATI to Early-ATI, NC had increases in Pol, PolyA, TatRev, and ratios of PolyA/Long (completion) and TatRev/Long (multiple-splicing) [all P<0.008] but not initiated (TAR) HIV transcripts (P=0.64). In contrast, PTC showed increases in Long, Pol, and PolyA (all P<0.03) but no change in TatRev, PolyA/Long, or TatRev/Long from Pre-ATI to Early-ATI. Early after ATI, PTC had lower levels of TAR, Long, Pol, PolyA, and PolyA/Long than NC (all P<0.026) and a trend toward lower TatRev (P=0.056). From Early-ATI to Late-ATI, the median VL and levels of all CA HIV RNAs tended to remain stable or increased in NC. In contrast, PTC showed a trend towards a decrease in median levels of Pol and PolyA from Early-ATI to Late-ATI (P=NS), such that there were no significant differences in any CA HIV RNA between Pre-ATI and Late-ATI. At the Late-ATI time point, PTC had lower VL (median 108 vs 11443 copies/ml) than NC and lower TAR, Long, Pol, PolyA, TatRev, PolyA/Long, and TatRev/PolyA (all P<0.05).

**Conclusion:** In NC, the transition from suppressive ART to viremia is mediated by increases in HIV transcriptional completion and splicing, not initiation. Compared to NC, PTC have lower levels of initiated HIV transcripts prior to ATI and are better able to limit HIV transcriptional completion and splicing after ATI. PTC may also have a decrease in completed HIV transcripts that begins early after ATI, suggesting an immune response targeting cells with completed HIV transcripts. Future strategies aimed at functional cure will likely need to limit HIV transcriptional completion and multiple splicing after ATI.

## 363 IMMUNOLOGICAL AND GLYCOMIC CORRELATES OF TIME-TO-HIV-REBOUND IN VIREMIC CONTROLLERS

**Yanhui Cai**[1], Steven G. Deeks[2], Liao Zhang[1], Leila B. Giron[3], Jane Koshy[3], Zongbo Shang[1], Susan Guo[1], Christiaan de Vries[1], Elena Vendrame[1], Devi SenGupta[1], Mohamed Abdel-Mohsen[3], Jeffrey Wallin[1]

*[1]Gilead Sciences, Inc, Foster City, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]Wistar Institute, Philadelphia, PA, USA*

**Background:** Analytic treatment interruption (ATI) is the most reliable way to evaluate the efficacy of potential HIV cure strategies but require lengthy and intensive monitoring. Identifying pre-ATI correlates of time-to-HIV-rebound (TTHR) after antiretroviral therapy (ART) cessation can significantly aid the development of a functional cure to HIV infection. We examined the associations between TTHR and pre-ATI immunological and glycomic profiles in a placebo-controlled Phase Ib study of the TLR7 agonist vesatolimod (VES).

**Methods:** We enrolled 25 HIV viremic controllers (pre-ART viral load 50-5000 copies/mL) who were ART-suppressed for ≥6 months. Seventeen participants received 10 biweekly doses of VES, and 8 received placebo, followed by an ATI phase for up to 48 weeks. Cell-associated immunological profiles were analyzed using flow cytometry. Plasma and isolated IgG glycomic profiles were analyzed using lectin array and capillary electrophoresis, respectively. Levels of biomarkers from baseline and last collection prior to ATI (pre-ATI) were used to determine associations with time when plasma viral load (VL) reached 200 copies/mL or 1000 copies/mL during ATI using the cox proportional hazard model. Nominal p values are reported.

**Results:** Higher pre-ATI frequency of activated CD69+ CD8+ T cells was associated with shorter time to reach 200 (p=0.003) and 1000 (p=0.002) copies/ml VL post-ATI. Baseline levels of several plasma glycomic markers were found to be associated with TTHR. Consistent with previously published data, higher baseline levels of plasma tri-sialylated N-glycans (A3G3S3) correlated with faster TTHR (200 copies/ml) (p=0.027). In addition, higher baseline levels of the pro-inflammatory GlcNac glycans in plasma (measured as binding to WGA lectin; p=0.008) and on IgG (p=0.04) correlated with shorter TTHR. Finally, higher plasma levels of GalNAc glycans (binding to MPA lectin) associated with longer TTHR (p=0.018).

**Conclusion:** Our exploratory analysis highlights specific host pro-inflammatory immunological and glycomic factors as potential correlates of the duration of viral control post-ART-cessation in HIV viremic controllers. Postulated host inflammatory pathways fostering post-ART viral rebound warrant further investigation into their prognostic and functional significance in larger independent cohorts, including those without a history of natural pre-ART viral control.

## 364 POST-TREATMENT CONTROLLERS MAINTAIN A LIMITED INTACT RESERVOIR AFTER ART INTERRUPTION

**Yijia Li**[1], Behzad Etemad[1], Meghan Melberg[1], Radwa Sharaf[1], Wendy Hartogensis[2], Ronald J. Bosch[3], Jeffrey Jacobson[4], Elizabeth Connick[5], Paul Volberding[2], Daniel J. Skiest[6], David M. Margolis[7], Steven G. Deeks[2], Michael M. Lederman[4], Frederick M. Hecht[2], Jonathan Li[1]

*[1]Brigham and Women's Hospital, Boston, MA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]Harvard TH Chan School of Public Health, Boston, MA, USA, [4]Case Western Reserve University, Cleveland, OH, USA, [5]University of Arizona, Tucson, AZ, USA, [6]University of Massachusetts, Worcester, MA, USA, [7]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** HIV post-treatment controllers (PTCs) are people with HIV who are able to maintain viral suppression after analytical treatment interruption (ATI). The dynamics of HIV-1 intact proviral reservoir size before and during ATI, however, remains underexplored. In this study, we evaluated HIV-1 proviral dynamics before and during ATI in PTCs and non-controllers (NCs).

**Methods:** The Control of HIV After Antiretroviral Medication Pause (CHAMP) study collected multiple treatment interruption trials from the AIDS Clinical Trials Group (ACTG) and the OPTIONS study. Only participants with reliably suppressed pre-ATI viral load were enrolled in those studies. PTCs were defined as those remaining off antiretroviral therapy (ART) for ≥24 weeks with post-ATI viral loads ≤400 copies/mL for at least 2/3 of the time points. We used intact proviral DNA assay (IPDA) to assess intact, defective, and total provirus before the ATI and at early and late time points during ATI. Near full length sequencing (NFL-seq) was performed on a subset of participants. We used the Wilcoxon test to assess differences between PTCs and NCs at each time point, with Benjamini-Hochberg correction for P values.

**Results:** 14 PTCs and 24 NCs were analyzed. Prior to ATI, PTCs had lower levels of intact (PTCs vs NCs, median 3.5 vs 14.7 intact copies/million PBMC, P=0.13) and defective provirus (median 19.8 vs 98.4 defective copies/million PBMC, P=0.01). During ATI, intact and defective proviral DNA levels remained largely stable in

the PTCs, while NCs demonstrated significant increases in the intact reservoir over time (Figure). The timing of ART initiation did not have a significant impact on ATI proviral dynamics. During early ATI, NCs also demonstrated increased proinflammatory cytokines that were significantly associated with levels of total and intact proviral DNA. A subset of participants had NFL-seq results (n=8), with a median of 57 sequences per participant. The correlation between total proviral DNA as measured by the IPDA and NFL-seq was r=0.62, P=0.1, while no significant correlation between intact proviral DNA measured by IPDA and NFL-seq. Compared to NFL-seq, IPDA reported a median 40-fold higher levels of intact and 20-fold higher levels of total proviral DNA.

**Conclusion:** ATI virologic control in PTCs extends to significantly lower levels of intact and total HIV-1 provirus compared to NCs based on the IPDA assay. Additional studies are needed to explore the mechanisms behind the reservoir control by PTCs.

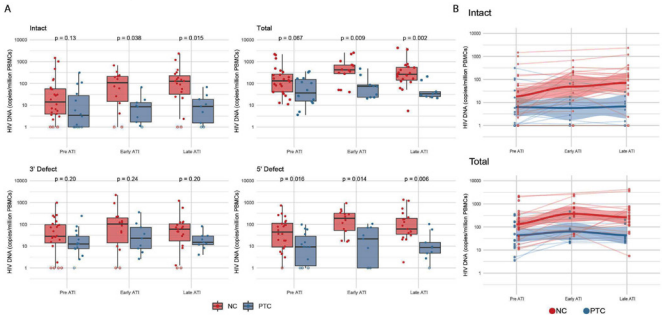



Figure Legend. (A)Proviral DNA levels measured by IPDA in post-treatment controllers (PTCs) and non-controllers (NCs). Open circles indicate levels below detection range. NCs had shorter ATI duration due to more rapid viral rebound. Median duration for early analytical treatment interruption (ATI) in PTCs was 12 weeks and 8 weeks in NCs. Median duration for late analytical treatment interruption (ATI) in PTCs was 60 weeks and 24 weeks in NCs. P values were calculated using the Wilcoxon test with Benjamini-Hochberg correction. (B) Temporal trend of intact and total proviral DNA in PTCs and NCs. Locally estimated scatterplot smoothing (Loess) regression was fitted for both groups and 95% confidence intervals were demonstrated.

## 365 LIMITED EVOLUTION OF THE VIRAL RESERVOIR IN A NONHUMAN PRIMATE MODEL OF ELITE CONTROL

New Investigator Scholar

**Kyle Rhodehouse**[1], Mithra R. Kumar[1], Emily J. Fray[1], Christine M. Fennessey[2], Pyone Aye[3], Faith Schiro[3], Amitinder Kaur[3], Marissa D. Fahlberg[3], Lara A. Doyle-Meyers[3], Jeffrey D. Lifson[2], Brandon Keele[2], James Hoxie[4], Nicholas Maness[3], Janet Siliciano[1], Robert Siliciano[1]

*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]AIDS and Cancer Virus Program, Frederick, MD, USA, [3]Tulane National Primate Research Center, Covington, LA, USA, [4]University of Pennsylvania, Philadelphia, PA, USA*

**Background:** Elite controllers, who control HIV infection in the absence of antiretroviral therapy, may hold the key to developing a cure. While this control effectively prevents high-level viremia and disease progression, the latent viral reservoirs persist in these individuals. In a recently described nonhuman primate model of elite control, pigtail macaques (PTMs) are infected with a variant of SIVmac239 (termed ΔGY) containing a 2 amino acid deletion in a conserved Env trafficking motif. After inoculation into PTMs, this virus produces high-level viremia, but is typically controlled to undetectable levels by host cellular immune responses in the absence of neutralizing antibodies. Animals remain clinically well for months-to-years. Because this phenotype resembles elite control of HIV in humans, we are investigating how the latent reservoir persists in this unique context.

**Methods:** We studied 4 male PTMs infected with ΔGY for >5 yrs. 3 maintained undetectable levels of plasma viral RNA (<15 copies/ml; elite controllers), while 1 exhibited low viral blips (>15 to <4300 copies/ml; partial controller). We used the SIV intact proviral DNA assay (IPDA) to measure the number of intact proviruses in blood and lymph nodes, 151 and 163 weeks post-infection, respectively, and developed a novel assay for full-length sequencing of SIV proviruses to analyze how individual proviruses persist.

**Results:** The number of intact proviruses was ~1 log lower in all 4 ΔGY-infected PTMs compared to SIVmac251-infected rhesus macaques on ART for 60 weeks (A. Bender et al. 2019). Intact proviruses from the partial controller contained mutations flanking the ΔGY mutation shown to confer improved fitness in vivo, as well as canonical and novel CTL escape mutations in immunodominant Gag and Tat epitopes restricted by MHC-I Mane-A*084, shared by these animals. In contrast, sequences from ΔGY-elite controllers were markedly conserved relative to the ΔGY inoculum, showing minimal evolution.

**Conclusion:** The smaller reservoirs of ΔGY-elite controllers relative to those of ART-treated noncontrollers is similar to reservoir sizes of human elite controllers compared to those of ART-treated noncontrollers (A. Kwaa et al. 2020). The presence of CTL escape mutations in the partial controller demonstrates that the CTL response can be a potent driver of virus evolution in reservoirs. In contrast, the minimal sequence changes in proviruses from ΔGY-elite controllers suggest a marked restriction of productive replication.

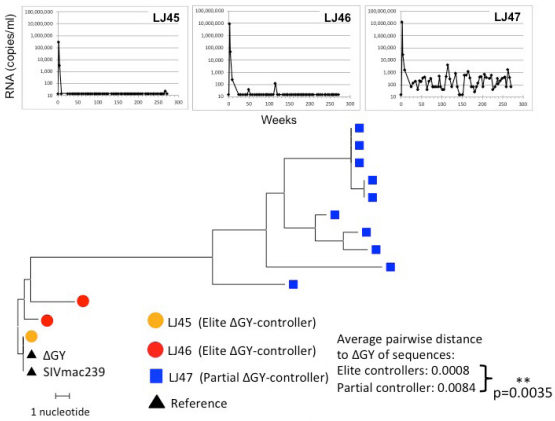



**Figure 1. Top panel-** Plasma viral RNA levels for 3 ΔGY-controlling PTMs. **Bottom panel-** A neighbor-joining tree of full length Env sequences obtained from peripheral lymph nodes 165 weeks post-infection, rooted to ΔGY. A branch distance of 1 nucleotide is shown. Sequences from the 3 PTMs shown in Top Panel are color coded with circles representing ΔGY elite controlling PTMs and squares representing the ΔGY partial controller. Triangles indicate reference sequences. Pairwise distance to the ΔGY reference sequence was calculated for each full length sequence. Statistical significance was measure using an unpaired t test.

## 366 CD8 RECOGNITION OF AUTOLOGOUS VIRUS IN HIV-ELITE CONTROLLERS DESPITE ESCAPE MUTATIONS

**Maria A Navarrete-Muñoz**[1], Alejandro Calderón[1], Ricardo Ramos[2], África Holguín[3], Alfonso Cabello Úbeda[4], Miguel Górgolas[4], José M. Benito[1], Norma Rallón[1]

*[1]Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain, [2]Parque Científico de Madrid, Madrid, Spain, [3]Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain, [4]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain*

**Background:** Escape mutations in HIV proviral sequence coding for epitopes of CD8 T cells response have been proposed as one of the reasons for the failure of the shock and kill strategy to purge the HIV reservoir. We previously reported the existence of mutations in CD8 epitopes in the viral reservoir, even in patients with spontaneous control of HIV (elite controllers). Herein, we have analysed the ability of HIV-specific CD8 response to recognize autologous epitopes from the viral reservoir, in two groups of HIV patients with different HIV replication control (spontaneously or through cART) and in a group of patients with uncontrolled HIV replication

**Methods:** Thirty HIV+ patients were included: 10 elite controllers (EC), 10 cART-suppressed (TX) and 10 cART-naive with high levels of HIV plasma viremia (TP).For each patient, the sequences of HIV-Gag CD8 epitopes restricted by the patient HLA-I haplotype were obtained from the proviral HIV-DNA of CD4 resting memory cells.CD8 T cells ability to respond to autologous Gag epitopes was examined using a boosted flow cytometry assay including IFNγ, MIP1β and TNFα production. Inter-group differences were assessed using non-parametric tests

**Results:** Prevalence (%) of mutated CD8 epitopes was 86[50-100], 57[48-82] and 64[50-71] in EC, TX and TP groups, respectively (p=0.52).All EC patients (100%) presented HIV-specific CD8 response against at least 1 autologous epitope, while the prevalence of this response in TX and TP groups was lower (70%, and 50%,respectively,p=0.085). The proportion of autologous epitopes that elicited a CD8 response was higher in EC vs to TX and TP (29%[25-29], 16%[0-42], and 3%[0-17] respectively;p=0.032).Moreover, there were no differences in the frequency of CD8 response between mutated and wild-type epitopes.Level of CD8 response was higher in EC vs to TX patients and similar to TP patients (0.43%[0.11-0.56], 0.095%[0.06-0.16], and 0.41%[0.32-0.8] respectively;p<0.0001) and this was independent of the type of epitope (mutated or wild-type).

**Conclusion:** Our results show that EC patients have an increased ability to recognize the autologous HIV viruses present in the viral reservoir despite the high prevalence of mutation in these epitopes, suggesting that the CD8 response of these patients could potentially be able to kill latently infected cells after reactivation with latency reversing agents. However, further studies

analyzing functional parameters of this CD8 response to autologous provirus are needed to ascertain this hypothesis.

## 367 HIV ENVELOPE DIVERSITY AND SENSITIVITY TO bNAbs ACROSS STAGES OF ACUTE AND EARLY HIV

**Laurie VanderVeen**[1], Brian Moldt[1], Lisa Selzer[2], Jiani Li[1], PC Parvangada[1], Jintanat Ananworanich[3], Trevor A. Crowell[4], Joseph J. Eron[5], Eric S. Daar[6], Richard H. Haubrich[1], Romas Geleziunas[1], Joshua Cyktor[7], John W. Mellors[7], Christian Callebaut[1]

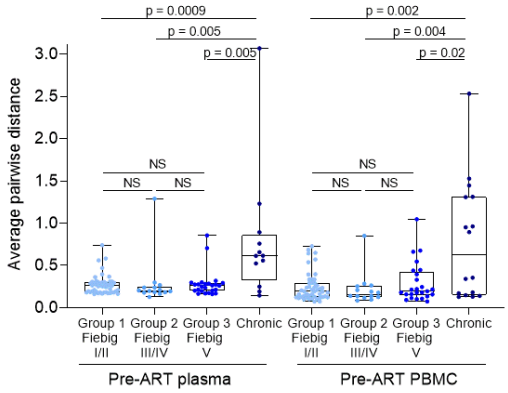
*[1]Gilead Sciences, Inc, Foster City, CA, USA, [2]Gilead Sciences, Inc, Foster City, CA, USA, [3]University of Amsterdam, Amsterdam, Netherlands, [4]US Military HIV Research Program, Silver Spring, MD, USA, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]Harbor–University of California Los Angeles Medical Center, Torrance, CA, USA, [7]University of Pittsburgh, Pittsburgh, PA, USA*

**Background:** Genetic diversity of the HIV envelope (env) complicates use of broadly neutralizing antibodies (bNAbs) for HIV treatment and cure. Antiretroviral therapy (ART) during acute or early HIV infection (AEHI) restricts reservoir size and diversity, increasing the likelihood of bNAb susceptibility. Successful treatment of ART-suppressed patients with bNAbs requires understanding the evolution of env diversity. We characterized env diversity and bNAb sensitivity at initiation of ART during AEHI and after ART suppression in a multinational prospective study.

**Methods:** Plasma and peripheral blood mononuclear cells (PBMC) were collected pre-ART and after 60 weeks from 89 participants in ACTG A5354 who initiated ART during protocol-defined AEHI: Fiebig I/II (Group 1), Fiebig III/IV (Group 2), or Fiebig V (Group 3). Viral env diversity was assessed by average pairwise distance analysis using a sliding window approach across env. AEHI participant env diversity was compared to virus from individuals in Gilead studies who initiated ART during chronic infection. Susceptibility to bNAbs elipovimab (EVM; PGT121 derivative) and 3BNC117 was determined using previously described env signatures.

**Results:** Env diversity in pre-ART plasma and PBMC virus was lower in participants initiating ART during AEHI than in chronic infection; there were no significant differences between Fiebig stages (Figure). Env diversity was not correlated with plasma HIV RNA levels at ART initiation. Compared to pre-ART, no significant difference in env diversity after 60 weeks of ART was observed in any group. The proportion of EVM-sensitive sequences did not differ in pre-ART plasma (42/87 [48%]), pre-ART PBMC (44/88 [50%]), and post-ART PBMC (40/79 [51%]) (p=.95). Susceptibility to bNAbs was comparable across groups, with 22/48 (46%) of Group 1, 7/14 (50%) of Group 2, and 13/25 (52%) of Group 3 sensitive to EVM in pre-ART plasma; sensitivities were maintained in pre- and post-ART PBMCs. Similar findings were observed for 3BNC117.

**Conclusion:** Env diversity was low in AEHI relative to chronic infection and did not differ significantly by Fiebig stage or after 60 weeks of ART. Similarly, susceptibility to bNAbs did not differ by stage of AEHI before or after ART. Collectively, these data argue against major differences in HIV diversity or bNAb sensitivity across AEHI stage or following more than one year of suppressive ART and suggest individuals who initiate ART during AEHI as a desirable population for bNAb treatment or cure trials.




HIV proviral DNA diversity assessed with sliding window (envelope gene)
Group comparisons by two-sided Wilcoxon rank sum test; NS,not significant

## 368 FUNCTIONAL MDSCs ARE MAINTAINED DURING ART AND PRECLUDE HIV-1 RESERVOIR REACTIVATION

New Investigator Scholar

**Ana Gallego Cortés**[1], Carla Serra[1], Judith Grau-Expósito[1], Joan Rey Cano[1], Jordi Navarro[2], Adrià Curran[2], Joaquin Burgos-Cibrian[2], Paula Suanzes[2], Vicenç Falcó[2], Meritxell Genescà[1], Maria José Buzón[1]

*[1]Vall d'Hebron Research Institute, Barcelona, Spain, [2]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain*

**Background:** In the past years, new therapeutic strategies aimed to deplete the HIV-latent infection by inducing viral reactivation have not been successful in vivo. The inability to reactivate and/or eliminate all HIV-infected cells could be explained by the presence of immune-regulatory mechanisms that inhibit viral reactivation and anti-HIV immune effector cells. We hypothesize that HIV reactivation might be hindered by myeloid-derived suppressor cells (MDSC), a heterogeneous population of immature myeloid cells with high immunosuppressive effects.

**Methods:** Samples from n=12 viremic (VIR) and n=14 ART-suppressed (ART) patients; and n=8 healthy donors (HD) were included in the phenotypic study. Frequency of 3 populations of MDSCs: CD33mid HLA-DRlow (CD3-, CD33mid, HLA-DRlow, CD11b+, CD14+/-); CD33mid HLA-DRmid (CD3-, CD33mid, HLA-DRmid, CD11b+, CD14+/-); and CD33high HLA-DRlow (CD3-, CD33high, HLA-DRlow, CD11b+, CD14+/-); was assessed by flow cytometry. The functional status of these MDSCs was quantified by the expression of Indolamine 2,3-dioxygenase (IDO) and Arginase-1 (ARG-1). Samples from n=18 ART patients and n=7 HD were used for functional studies in which virally-reactivated CD4 T cells and MDSCs subpopulations were co-cultured. Viral reactivation and cell activation were assessed by intracellular p24 and surface CD69 staining, respectively. HIV-DNA and cell-associated HIV-RNA (caHIV-RNA) were quantified by qPCR.

**Results:** Both VIR and ART patients showed significantly higher proportions of MDSCs expressing IDO and ARG-1 compared to HD. The expansion of CD33mid HLA-DRlow IDO+ and CD33mid HLA-DRlow ARG-1+ MDSCs in VIR patients was the most noticeable (16.1% and 4.1% compared to 4.5% and 1.9% in HD), and the levels of CD33mid HLA-DRlow IDO+ positively correlated with caHIV-RNA (rho=0.66 p=0.049). In ART patients, neither CD33mid HLA-DRlow IDO+ nor CD33mid HLA-DRlow ARG-1+ percentages were normalized to HD levels (11.8% and 3.2%) irrespectively of months under treatment. Functional assays showed that CD33mid HLA-DRlow MDSCs significantly reduced HIV reactivation from the latent reservoir ex-vivo (p=0.009), which was associated with a slight but consistent reduction in cell activation levels (p=0.023).

**Conclusion:** Overall, we found that HIV infection expands CD33mid HLA-DRlow IDO+ and ARG-1+ MDSCs subsets, which are not normalized after ART initiation, and significantly preclude viral reactivation. Finding new therapeutic strategies targeting MDSCs could significantly impact the HIV reservoir.

## 369 ROVER: REDIRECTOR OF VACCINE-INDUCED EFFECTOR RESPONSES FOR HIV-1 TARGET CELL KILLING

New Investigator Scholar

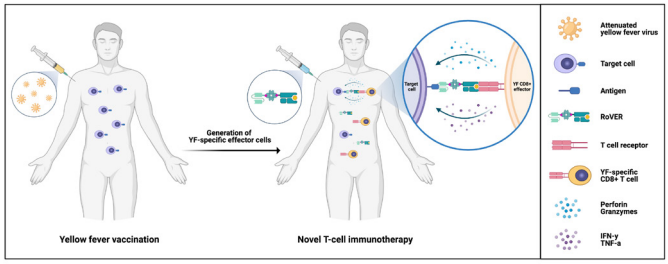
**Christina V. Konrad**[1], Emma F. Iversen[1], Jesper D. Gunst[2], Ida Monrad[2], Lars Østergaard[2], Ole Søgaard[2], Mariane H. Schleimann[2], Martin Tolstrup[2]

*[1]Aarhus University, Aarhus, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark*

**Background:** Cytotoxic T lymphocytes (CTLs) are potent killers of virus infected cells. In most HIV-1 infected persons, HIV-specific CTLs display an exhausted phenotype with limited capacity to control or eliminate HIV-1 infection. Immunotherapy with Chimeric Antigen Receptor-modified CTLs is a promising technology but is limited by costs, requirements for genetic manipulation and ex vivo expansion. We have developed a novel immunotherapy concept in which potent vaccine-induced effector CTLs are redirected to target and eliminate HIV-1-infected cells using a bispecific molecule (RoVER) comprising two functionally distinct domains: 1) a scFv-domain targeting HIV Env, and 2) an HLA-I molecule with a vaccine epitope.

**Methods:** Following YF-17D (Stamaril, Novartis) vaccination of 52 healthy volunteers (NCT04083430), single-epitope yellow fever-specific CTL responses were quantified by tetramer staining and multicolor flow cytometry. In cell killing assays, the ability of RoVER to mediate killing of target cells upon exposure to CTLs obtained from study participants 21 days post vaccination was assessed and compared to an FDA approved CD19 BiTE; blinatumomab. As target cells, both Raji-Env and autologous CD4+ cells infected in vitro with a full-length HIV-1-eGFP were used. Moreover, secreted IFN-γ, granzymes, perforin and TNF-a were analyzed by mesoscale multiplex assays.

**Results:** YF-17D vaccination induced strong epitope-specific CTL responses in all study participants. In HLA*A2 individuals, a mean of 2.8% of CTLs (range 0.1-10.3%) targeted the immunodominant NS4B 214-222 epitope. RoVER-mediated redirection of NS4B-specific effector CTLs to Raji-Env or HIV-eGFP-infected autologous CD4 target cells resulted in 32% and 65% killing, respectively, at E:T 3:1. Target cell killing was associated with pronounced secretion of IFN-γ. In contrast, no target killing was observed using autologous CTLs obtained prior to YF-17D vaccination or without exposure to RoVER. Moreover, RoVER-mediated target cell killing could be achieved using different HLA-molecules and epitopes.
**Conclusion:** We have developed a novel immunotherapy concept in which epitope-specific CTLs induced by simple vaccination can be redirected toward HIV-infected cells by RoVER linking. Advantages of this novel technology are that it obviates the need for ex vivo modification and expansion. Moreover, this technology is highly specific and easily adapted to recognize any cell surface antigen of interest and thus holds great promise for various diseases.




## 370 TARGETED DELIVERY OF BCL2 INHIBITORS SENSITIZES HIV+ CELLS TO ELIMINATION BY CTL

**Andrea Gramatica**[1], Ozgun Kocabiyik[2], Rachel S. Resop[3], Ali Danesh[1], Dennis C. Copertino[1], Alberto Bosque[3], Darrell Irvine[2], R. Brad Jones[1]
*[1]Weill Cornell Medicine, New York, NY, USA, [2]Massachusetts Institute of Technology, Cambridge, MA, USA, [3]George Washington University, Washington, DC, USA*

**Background:** We have previously demonstrated that cells harboring replication competent virus in ARV-treated individuals are resistant to cytotoxic T-lymphocyte (CTL)-mediated killing, in part because of over-expression of BCL-2. Treatment of ex vivo CD4+ T-cells with the BCL-2 antagonist ABT199 sensitized infected cells to killing by CTLs, reducing the HIV reservoirs. ABT199 is the active agent in Venetoclax, an approved FDA drug. Here, we aimed to mitigate the significant toxicity profile of ABT199 by developing a novel nanoemulsion(NEs)-based approach for focusing delivery to HIV- infected cells.
**Methods:** Transcriptional profiling of infected versus uninfected CD4+ T-cells was used to identify a list of surface proteins that enrich for HIV+ cells. Expression of these markers was compared between Gag+ and Gag- cells in vitro and in tissues of HIV-infected 'participant-derived xenograft' mice. NEs were generated with a maleimide end-group for antibody decoration and a bodipy-cholesteryl ester to allow for assessment of targeting using fluorescence microscopy and flow cytometry.
**Results:** Flow cytometric analysis of tissues isolated from HIV-infected mice revealed consistently higher expression of CD69 and CD127 on infected versus uninfected cells, and CD69 was prioritized as a target. NEs were loaded with ABT199, and when conjugated to anti-CD69 preferentially targeted CD69+ CD4+ T-cells, resulting in cellular uptake as assessed by confocal microscopy, while such uptake was not observed for non-antibody-targeted NEs. We then demonstrated that Gag+ cells internalize between 1.8- and 2.4-fold more NEs than Gag- cells. This targeted delivery was associated with less bystander toxicity compared to treatment with free ABT199, but did not significantly reduced %Gag+ cells, neither did treatment with antiCD69-NEs alone or CTLs+ABT199. However, a much higher degree of infected cell killing (approximately 3 times more) was achieved when cells were treated with both antiCD69-NEs and autologous CTLs.
**Conclusion:** Our results demonstrate that CD69-targeted ABT199-NEs can support CTLs in eliminating HIV-infected cells. While more in vivo studies are necessary, this novel strategy has the potential to harness the ability of ABT199 to sensitize viral reservoirs to elimination, while reducing the toxic profile of systemic perfusion with ABT199.

## 371 THE LATENT SIV RESERVOIR IS ESTABLISHED INDEPENDENT OF CYTOTOXIC T LYMPHOCYTE CONTROL

New Investigator Scholar

**Maura Statzu**[1], Andrew Wong[1], Julia B. McBrien[1], Jin Wang[2], Miles P. Davenport[2], Brandon Keele[3], Thomas H. Vanderford[1], Ann Chahroudi[4], Mirko Paiardini[1], Guido Silvestri[1], Deanna Kulpa[1]
*[1]Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA, [2]Infection Analytics Program, Kirby Institute for Infection and Immunity, University of New South Wales, Sydney, Australia, [3]AIDS and Cancer Virus Program, Frederick National Laboratory, Frederick, MD, USA, [4]Emory University, Atlanta, GA, USA*

**Background:** The persistence of HIV infection under anti-retroviral therapy (ART) is due to a reservoir of latently-infected cells harboring integrated replication-competent virus which cause rebound viremia after analytic treatment interruption (ATI). However, whether these latently infected cells are formed directly after integration or following a phase of productive infection remains unclear. In this study, we addressed this question in SIV-infected rhesus macaques (RM) by performing experimental CD8+ depletion either prior to infection or prior to ART initiation (day-12 post-infection).
**Methods:** A total of 21 RM were infected with a barcoded SIVmac239 and ART was initiated 2 weeks post-infection. 8 RM received the CD8α-depleting antibody MT-807R1 before SIV infection, 8 RM were CD8 depleted just prior to ART initiation, and 5 SIV-infected ART treated RM served as the control group. After 50 weeks on ART, all RM underwent ATI and were followed for 12 weeks. SIV expression was monitored by plasma viral load, as well as cell-associated (CA)-RNA in peripheral blood (PB) and lymph node (LN). The viral reservoir size was assessed by total SIV CA-DNA in PB and LN. Mathematical modeling was used to assess the decay kinetics of virus expression.
**Results:** As expected, we found that CD8+ depletion resulted in slower decline of plasma viremia, corresponding to a slower decline in SIV CA-RNA frequency and higher barcode diversity in plasma, therefore indicating that CTLs reduce the average lifespan of productively infected cells during the acute phase of SIV infection. In addition, we observed an increased ratio of viral CA-RNA:CA-DNA in CD8+ depleted animals. Significantly, CD8+ depletion did not change the size of the virus reservoir measured either directly, as total CA-DNA, or indirectly, as kinetics of virus rebound after ART interruption.
**Conclusion:** Together, these data support the role of CD8+ T cells, presumably through cytotoxic T lymphocyte function, in decreasing the average lifespan of short-lived productively infected cells during acute infection. By contrast, long-lived infected cells were not significantly impacted by the presence of CD8+ T cells, supporting the hypothesis that long-lived infected cells establish the persistent reservoir independent of cytolytic T cell control. These data highlight the importance of understanding the mechanisms by which cytolytic and non-cytolytic CD8+ T cell functions impact the establishment and maintenance of the virus reservoir under ART.

## 372 AUTOLOGOUS NEUTRALIZATION OF HIV RESERVOIR OUTGROWTH IS STABLE OVER TIME DURING ART

New Investigator Scholar

**Joseph Varriale**[1], Subul Beg[1], Natalie McMyn[1], Kwan Pui Chan[1], Francesco R. Simonetti[1], Kenneth Lynn[2], Pablo Tebas[2], Ian Frank[2], Karam Mounzer[3], Katharine J. Bar[2], Michael Seaman[4], Robert Siliciano[1], Janet Siliciano[1]
*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]Philadelphia FIGHT, Philadelphia, PA, USA, [4]Beth Israel Deaconess Medical Center, Boston, MA, USA*

**Background:** During untreated HIV-1 infection, rapid viral evolution allows escape from neutralizing antibodies. Using a modified quantitative viral outgrowth assay, we previously demonstrated that outgrowth of a substantial but variable fraction of reservoir viruses is blocked by autologous contemporaneous IgG (Bertagnolli et al.,PNAS 2020). However, the dynamics of aNAb titer and activity over time are not well understood. We hypothesized that suppression of viral outgrowth due to aNAbs is maintained over time in individuals on suppressive ART.
**Methods:** We obtained follow up leukapheresis samples from individuals in the cohort described in Bertagnolli et al. 2020 and performed modified quantitative viral outgrowth assays on resting CD4+ T cells (rCD4s) from follow up timepoints using contemporaneous autologous neutralizing antibodies (aNAbs), purified from contemporaneous plasma. Outgrowth viruses were analyzed by full-length env sequencing. In addition, aNAbs from the follow up timepoints, and a panel of clinically relevant broadly neutralizing antibodies (bNAbs) were

tested for neutralization activity against pseudoviruses derived from earlier time points in a TZM-bl based assay.

**Results:** In longitudinal analysis with resting CD4 cells and aNAb, suppression of outgrowth in the QVOA by aNAbs was maintained or enhanced two years following initial sampling. Moreover, analysis of direct neutralization against individual viral variants from five individuals reveals an overall maintenance of neutralization capacity of aNAbs over a time scale ranging from 2-6 years. We have also identified unique neutralization activity of clinically relevant bNAbs to aNAb resistant virus. Full length env sequencing and pseudovirus neutralization assays with the env sequences have provided insights into the epitopes targeted by aNAbs and into the question of whether aNAb-resistant viruses are susceptible to clinically relevant bNAbs.

**Conclusion:** We determined that suppression of outgrowth and aNAb neutralization titers against autologous viruses from the latent reservoir are maintained over a period of at least 2-6 years, and in some individuals have increased over time. Moreover, aNAb resistant virus from some individuals are specifically susceptible to individual bNAbs. This study provides evidence that aNAbs are effective at suppressing outgrowth of a subset of reservoir viruses over prolonged time interval. Thus, cure efforts should focus on aNAb-resistant viruses, some of which may be targeted by bNAbs.

## 373 SARS-CoV-2 mRNA VACCINATION EXPOSES LATENT HIV TO Nef-SPECIFIC CD8+ T CELLS

**Eva Stevenson**[1], Sandra Terry[1], Dennis C. Copertino[1], Louise Leyre[1], Adam R. Ward[1], Pragya Khadka[1], Kevin Bernard[1], Grant Ellsworth[1], Carrie Johnston[1], Marina Caskey[1], Christian Gaebler[1], Timothy Wilkin[1], Guinevere Q. Lee[1], R Brad Jones[1]

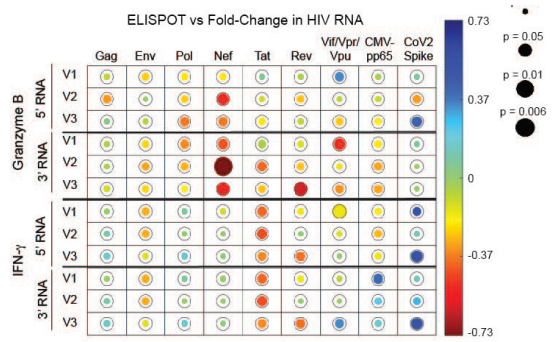
*[1]Weill Cornell Medicine, New York, NY, USA*

**Background:** The kinetics and functional profiles (granzyme-B production) of HIV-specific T-cell responses support that those targeting the early viral gene product Nef disproportionately recognize residual antigen expression during long-term antiretroviral therapy (ART). Here, we leveraged this insight to test whether SARS-CoV2 mRNA vaccines – which activate TLR and inflammatory signaling pathways - would reactivate latent HIV, stimulating T-cell responses with these characteristics.

**Methods:** T-cell responses to individual HIV gene products were measured by IFN-g or granzyme B ELISPOT, and by activation induced marker (AIM) assays at baseline and ~2 weeks after SARS-CoV-2 mRNA vaccine prime and boost, in 13 long-term ART treated adults. Total and unspliced HIV mRNA, as well as intact and defective (IPDA) HIV DNA were measured in parallel by digital droplet PCR (ddPCR).

**Results:** We observed transient increases Nef-specific T-cell responses following vaccine prime by granzyme B ELISPOT (3.1-fold increase, p=0.002) and a trend by AIM assay (1.5-fold increase, p=0.06). Such increases were not observed in granzyme B responses to late gene products nor in any IFN-g responses. Both unspliced and total HIV mRNA decreased significantly across the study, unspliced - 1.6-fold decrease p = 0.03; total - 1.5-fold decrease p = 0.05. Changes in total HIV mRNA correlated inversely with Nef-specific granzyme B-producing (spearman's ρ = -0.73, p = 0.006) and Nef-specific CD8+ AIM T-cell responses (ρ = -0.76, p = 0.006) following vaccine prime. These reductions in HIV RNA were not accompanied by significant changes in total or intact HIV DNA.

**Conclusion:** Consistent with our hypothesis, a restricted profile of HIV-specific T-cell responses showed significant increases following SARS-CoV-2 vaccine prime, each of which were then correlated with reductions in HIV RNA. This supports that vaccination promoted productive interactions between Nef-specific CTL and HIV-infected cells in vivo. We propose three scenarios for why this was not reflected in reductions in intact or total HIV DNA: i) meaningful depletions in inducible proviruses occurred but were lost against the background of non-inducible proviruses ii) interactions with CTL involved only a fraction of inducible proviruses, or iii) substantive proviral depletions occurred, but were counterbalanced by clonal expansion of HIV-infected cells.




## 374 HODHBt SYNERGIZES WITH IL-15 TO ENHANCE THE CYTOTOXIC CAPACITY OF HIV-SPECIFIC CTL

**Dennis C. Copertino**[1], Carissa Stover[2], Amanda Macedo[2], Alberto Bosque[2], R Brad Jones[1]

*[1]Weill Cornell Medicine, New York, NY, USA, [2]George Washington University, Washington, DC, USA*

**Background:** Although effective against models of HIV latency, 'shock and kill' approaches aimed at reducing HIV reservoirs have not yet yielded this outcome in clinical trials, pointing to the need for novel and more potent therapeutic agents. 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HODHBt), an enhancer of STAT activation, increases occupancy of the transcription factor STAT5 on the HIV LTR thereby reactivating latent HIV in CD4+ T-cells. We have previously shown that HODHBt enhances IL-15 mediated reactivation in cells isolated from aviremic participants. STAT5 can also enhance CD8+ T-cell effector functions by transducing IL-15 signaling. Since HODHBt enhances STAT5 activation, we hypothesized that HODHBt would act synergistically with IL-15 to enhance cytotoxic function (GZMB release) of ex vivo HIV-specific CD8+ T-cells from ART treated individuals.

**Methods:** Granzyme B (GZMB) ELISpots were performed on PBMCs from 14 people living with HIV in the who had been on suppressive ART for an average of 10.9 years (range, 7.4-18). Cells were stimulated with peptide pools spanning Gag, Pol, Nef, or Env, CMVpp65, with or without 1 ng/ml IL-15 and/or 50 ug/ml HODHBt. Supernatants were collected and cytokine secretion was analyzed using the CorPlex Human Cytokine Panel 1 10-Plex array (IFN-ϒ, IL-1b, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-22 and TNF-α).

**Results:** HIV-specific GZMB-releasing responses were enhanced by treatment with HODHBt in combination with IL-15, relative to medium only as follows: (mean/mean) Gag - 6.8-fold (p=0.005), Pol - 6.8-fold (p=0.005), Nef - 12.8-fold (p<0.001), and Env - 3.7-fold (p=0.438, ns). These were substantially increased relative to enhancements with IL-15 alone (median IL-15+HODHBt/median IL-15+DMSO) Gag - 2.4-fold (p = 0.0001), Pol - 1.8-fold, (p=0.0009), Nef - 4.3-fold, (p=0.0002), and Env - 2.6-fold, (p=0.0005). HODHBt alone did not increase background (no peptide) above IL-15 alone. Across all conditions and peptides, except CMV, GZMB was significantly positively correlated with IFNγ (r= 0.89, p<0.0001) and IL22 (r=0.73, p<0.001).

**Conclusion:** In addition to its LRA potential, we show that HODHBt synergizes with IL-15 to markedly enhance HIV-specific cytotoxic T-cell responses in ex vivo PBMCs from ART-treated donors. Our results highlight that pharmacologic enhancement of IL-15 mediated STAT activation can be a therapeutic strategy with the potential to enhance both the 'shock' and the 'kill' components of strategies aimed at depleting HIV reservoirs.

## 375 ALTERED CELL CYCLING AND APOPTOSIS IN COLONIC MUCOSA OF IMMUNOLOGICAL NONRESPONDERS

**Mari Kaarboe**[1], Mingyi Yang[1], Malin H. Meyer-Myklestad[2], Arvind Y. Sundaram[2], Asle W. Medhus[1], Birgitte Stiksrud[1], Anne Ma Dyrhol-Riise[1], Dag Kvale[2], Johannes R. Hov[1], Marius Trøseid[1], Pål Aukrust[1], Magnar Bjørås[3], Dag Henrik Reikvam[1]

*[1]Oslo University Hospital, Oslo, Norway, [2]University of Oslo, Oslo, Norway, [3]Norwegian University of Science and Technology, Trondheim, Norway*

**Background:** Approximately 15% of people living with HIV (PLHIV) on antiretroviral therapy (ART) and persistent viral suppression fail to restore CD4+ T cell levels. These immunological nonresponders (INR) have increased risk of non-AIDS-related morbidity and mortality. The etiology of the INR phenotype remains unknown. We have recently shown that compared to immunological

responders (IR) and HIV negative controls, INR have signs of increased enterocyte damage and gut mucosal immune dysfunction restricted to colon.
**Methods:** We performed mRNA sequencing and global proteome analyses by mass spectrometry (MS) of gut mucosal biopsies from sigmoid colon and terminal ileum of INR (ART>4 years with HIV RNA <50 copies/ml and CD4 count <400 cells/μL for >3.5 years), 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 (n=5 of each group). Differential expression analyses were performed using negative binomial GLM fitting and Wald test for RNA-sequencing and empirical Bayes statistics test for analyses of proteomics MS data. Targeted differentially expressed genes were assessed by quantitative PCR.
**Results:** In the sigmoid colon, approximately 3300 mRNA transcripts were significantly differentially expressed in INR compared to IR. In contrast, no differential expression was observed between INR and IR in terminal ileum. We detected about 3700 proteins by global proteomic analyses that were evaluated for differential expression. Consistently, global proteomic analyses showed a higher level of differential regulation between INR and IR in colon than in terminal ileum (12 versus 4). In the colon, the protein periostin, involved in cell survival, and Musashi RNA binding protein 2 (MSI2), involved in cell cycle regulation, were both identified as two of the most differentially downregulated proteins in INR compared to IR. The apoptotic factor protein CASP3 were highly upregulated in colon of INR compared to IR. There was no differential regulation of these proteins in the terminal ileum.
**Conclusion:** Sigmoid colon, as opposed to terminal ileum, is implicated as an anatomic site linked to mechanisms causing complete immune recovery in PLHIV. The differentially regulated genes and proteins identified in sigmoid colon may contribute to the INR phenotype through reduced cell survival, cell cycle regulation and increased apoptosis. These factors may be candidates for adjuvant therapy to improve the prognosis and quality of life for PLHIV.

## 376 IMPACT OF TREATMENT INTERRUPTION ON COLONIC MUCOSA IN ACUTELY TREATED PARTICIPANTS

Late Breaking

**Alexandra Schuetz**[1], Catherine Brands[2], David Morcock[2], Donn J. Colby[3], Trevor A. Crowell[3], Rungsun Rerknimitr[4], Carlo Sacdalan[5], Suteeraporn Pinyakorn[3], Yuwadee Phuang-Ngern[1], Brandon Keele[2], Jeffrey D. Lifson[2], Jintanat Ananworanich[6], Denise C. Hsu[3], Claire Deleage[2]
*[1]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [2]AIDS and Cancer Virus Program, Frederick, MD, USA, [3]Walter Reed Army Institute of Research, Silver Spring, MD, USA, [4]Chulalongkorn University, Bangkok, Thailand, [5]Thai Red Cross AIDS Research Center, Bangkok, Thailand, [6]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands*

**Background:** Despite antiretroviral therapy (ART) initiation during acute HIV infection and viral suppression for years, most individuals experience viral rebound shortly after treatment interruption. The major obstacles to HIV cure are tissue reservoirs that are established early during infection. We had the unique opportunity to analyze sigmoid colon biopsies prior to and during analytical treatment interruption (ATI) from participants who initiated ART during acute HIV infection at Fiebig I-III.
**Methods:** A total of twelve individuals with plasma viral suppression from two ATI trials, who received no intervention (n=5) or the VRC01 mAb during ATI (n=7) were included. Participants underwent sigmoidoscopy at baseline (while on ART for an average of 3.3 years, n=12), at the time of viral rebound after ATI (n=6, 2 of 6 were VRC01 recipients) and 6-12 months after ART resumption (n=6, 2 of 6 were VRC01 recipients). We performed immunohistochemistry (IHC) and flow cytometry to assess immune cell numbers and frequency (CD4, CD8, CD68, CD163), quantify activation and inflammatory markers (Ki67, Mx1, TNF∝) and localization and phenotype of vRNA+ cells by in situ hybridization (RNAscope). Changes from baseline ATI to rebound were tested using Wilcoxon signed-rank test.
**Results:** At baseline, 4 (3 FiebigI and 1 FiebigII) of 12 participants (33%) had detectable vRNA+/CD4+ T cells within the lamina propria (LP) (Fig.1A) or lymphoid aggregates (LA) despite undetectable (<20cp/ml) plasma viral load (pVL). At viral rebound, a median (IQR) of 30 (24-35) days after ATI, the median (IQR) pVL was 2380 (1019-3843) cp/ml and all participants (n=6) had CD4+ T cells harboring vRNA in colonic biopsies. We observed an increase in CD4+ T cells within the LP using IHC (1.35 to 2.02 %CD4+T cell/Area; p=0.028) (Fig.1B) without significant changes in the number of myeloid (CD68+ CD163+) or CD8+ T cells. We also found an increase in activated HLA-DR+CD38+ colonic CD8+ T cell by flow cytometry (9 to 17.3%, p=0.043). No vRNA+ cells were detected using RNAscope within the biopsies taken 6-12 months post ART resumption.
**Conclusion:** We observed a significant increase in colonic CD4+ T cells within the LP and CD8+ T cell activation at the time of rebound. Despite plasma viral suppression, vRNA+ cells were found in a third of participants while on ART and detected in all at rebound, reinforcing the importance of the GALT as a likely viral reservoir site and an essential site of viral replication during treatment interruption.

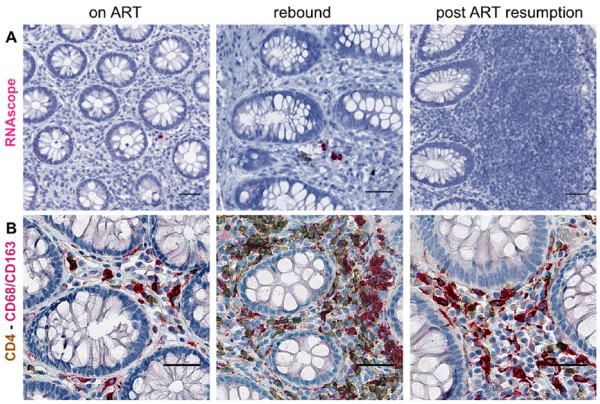



**Figure 1**: Representative images of RNAscope (A) and CD4/Myeloid cells (B) by IHC in gut biopsies of participants prior to and during ATI.

## 377 HIV-1 RESERVOIRS ESTABLISHED PRIOR TO THERAPY CONTRIBUTE TO REBOUND VIRUS

New Investigator Scholar

**Katie Fisher**[1], Xiao Qian Wang[1], Ashley Lee[1], Vincent Morcilla[1], Anneke de Vries[1], Eunok Lee[1], John-Sebastian Eden[1], Steven G. Deeks[2], Anthony Kelleher[3], Sarah Palmer[1]
*[1]The Westmead Institute for Medical Research, Westmead, Australia, [2]University of California San Francisco, San Francisco, CA, USA, [3]Kirby Institute, Sydney, Australia*

**Background:** Genetically-characterising rebound virus during analytical treatment interruptions (ATI) will further our understanding of the persistent HIV-1 reservoir that is the barrier to a cure. Therefore, we employed a novel long-range RNA sequencing method to investigate the genetic composition of HIV-1 virions within ATI plasma samples from participants treated during acute infection.
**Methods:** First, we employed the plasma-derived RNA using long-range sequencing (PRLS) assay to sequence near-full-length HIV-1 RNA (gag-3'; 8.3kb) from the pre-ART plasma, and the full-length individual proviral sequencing (FLIPS) assay (9kb) to sequence proviral DNA genomes from paired pre-ART PBMC samples from 3 individuals. Next, we used the int-3' PRLS assay (5kb) to sequence RNA genomes from plasma samples with lower viral loads collected during an ATI. For comparison, we trimmed all sequences to a ~4.7 kb region overlapping the gag-3', FLIPS and int-3' amplicons (trimmed int-3' region).
**Results:** For all 3 participants, the proportion of 100% identical sequences within the trimmed int-3' region was higher in the ATI plasma sequences (mean: 32.8%) compared to the pre-ART plasma sequences (mean: 13.3%), though this did not reach statistical significance (p=0.25). In addition, 87% (mean proportion) of genomes from the ATI plasma samples were genetically-intact, which is higher than the genetically-intact genomes identified within the pre-ART plasma (65%: mean proportion). When we compared the trimmed int-3' sequences from all compartments and timepoints, we identified examples of ATI plasma-derived sequences that were 100% identical to pre-ART plasma and/or PBMC sequences for all three participants. All sequences we identified as 100% identical to another sequence in the trimmed int-3' region were genetically-intact in this region. For 2 participants, we also identified an ATI plasma-derived sequence that was 100% identical to a group of pre-ART plasma-derived and PBMC-derived sequences in the trimmed int-3' region, with at least 2 of these pre-ART plasma and PBMC sequences being 100% identical and genetically-intact in their respective near-full-length sequences.
**Conclusion:** Employing the int-3' PRLS assay, we found that ATI plasma-derived sequences were clonal and genetically-intact. Several sequences from the ATI plasma samples were identical to viral sequences from pre-ART plasma and PBMC samples, indicating that HIV-1 reservoirs established prior to therapy contribute to viral rebound during an ATI.

**378 Vpr SHAPES THE PROVIRAL LANDSCAPE AND POLYCLONAL HIV-1 REACTIVATION PATTERNS IN VITRO**

**Edmond Atindaana**[1], Sarah Emery[1], Cleo Burnett[1], Jake Pitcher[1], Jeffrey M. Kidd[1], Alice Telesnitsky[1]
[1]*University of Michigan, Ann Arbor, MI, USA*

**Background:** Cell culture models suggest that the HIV-1 viral protein R (Vpr) is dispensable for latency establishment. However, whether Vpr affects the persistent proviral landscape and responsiveness to latency reversing agents (LRAs) is unclear.
**Methods:** Here, integration site landscape, clonal dynamics, and latency reversal effects of Vpr were studied by comparing barcoded vpr+ and vpr- populations arising after infection of jurkat cells in vitro.
**Results:** The results showed that individual integrant clones differed in fractions of LTR-active daughter cells: some clones gave rise to few to no LTR-active cells while for others almost all daughter cells were LTR-active. Integrant clones with at least 60% LTR-active cells (high LTR-active clones) contained proviruses positioned closer to preexisting enhancers (H3K27ac) and promoters (H3K4me3) than clones with <30% LTR-active cells (low LTR-active clones). Comparing vpr+ and vpr- populations revealed that the vpr+ population was depleted of high LTR-active clones. Complementing vpr-defective proviruses by transduction with vpr 16 days after infection led to rapid loss of high LTR-active clones, indicating that the effect of Vpr on proviral populations occurs post-integration. Comparing vpr+ and vpr- integration sites revealed that predominant vpr+ proviruses were farther from enhancers and promoters. Correspondingly, distances to these marks among previously reported intact HIV proviruses in ART-suppressed patients were more similar to those in the vpr+ pool than to vpr- integrants. To compare latency reactivation agent (LRA) responsiveness, the LRAs prostratin and JQ1 were applied separately or in combination. vpr+ and vpr- population-wide trends were similar, but combination treatment reduced virion release in a subset of vpr- clones relative to when LRAs were applied separately, an effect not observed in vpr+ pools.
**Conclusion:** Together, these observations highlight the importance of Vpr to proviral population dynamics, integration site landscapes, and responsiveness to latency reversing agents.

**379 SIZE AND ACTIVITY OF THE HIV RESERVOIR PREDICT REBOUND TIMING AFTER ART INTERRUPTION**

**Jonathan Li**[1], Autumn Kittilson[1], Meghan Melberg[1], Elizabeth R. Wonderlich[2], Jennifer Kinslow[3], Evgenia Aga[4], Ronald J. Bosch[4], Robert Coombs[5], Steven G. Deeks[6], Rajesh T. Gandhi[7], Michael P. Busch[8], Alan Landay[3], Bernard J. Macatangay[9], Davey M. Smith[10]
[1]*Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA,* [2]*Southern Research, Frederick, MD, USA,* [3]*Rush University, Chicago, IL, USA,* [4]*Harvard TH Chan School of Public Health, Boston, MA, USA,* [5]*University of Washington, Seattle, WA, USA,* [6]*University of California San Francisco, San Francisco, CA, USA,* [7]*Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA,* [8]*Vitalant Research Institute, San Francisco, CA, USA,* [9]*University of Pittsburgh, Pittsburgh, PA, USA,* [10]*University of California San Diego, San Diego, CA, USA*

**Background:** The A5345 prospective treatment interruption (TI) study in the setting of modern ART previously demonstrated a modest delay in HIV rebound in those who had initiated ART during early infection. From A5345, we sought to identify pre-TI predictors of time to HIV rebound that could be crucial for designing and evaluating interventions for HIV remission.
**Methods:** 5345 participants initiated ART during chronic (N=33) or early (N=12) HIV infection with ≥2 years of suppressive ART, and restarted ART if two viral loads ≥1,000 copies/mL after TI. Viral reservoir markers quantified pre-TI included: unspliced cell-associated RNA (CA-RNA), total HIV DNA (total-DNA), intact proviral DNA (IPD) by the IPDA, integrase single-copy assay (iSCA), and infectious units/million rCD4 cells (IUPM) by viral outgrowth assay. We assessed associations between reservoir measures with time to HIV rebound and cellular and humoral immune responses.
**Results:** Early-treated participants had smaller and less transcriptionally active HIV reservoirs as reflected by significantly lower levels of CA-RNA (9-fold), total-DNA (3-fold), IPD (4-fold) and IUPM (1.4-fold) compared to chronic-treated participants. IPD correlated with total-DNA and IUPM (Spearman r=0.45, P=0.004 for both). As part of the primary objective, we found that lower reservoir activity was modestly associated with a delay in HIV rebound (CA-RNA: r=-0.26, P=0.08). The strongest predictor of time to HIV rebound was IPD in chronic-treated participants (r=-0.37, P=0.04) and iSCA in early-treated participants (r=-0.68, P=0.02). Amongst all participants, a higher percentage of HIV gag-specific CD8+ T cell cytotoxic response (CD107a) was associated with a lower IPD (r=-0.37, P=0.02). In early-treated participants, a higher percentage of CD8+ T cells expressing ≥2 effector cytokines was also associated with lower IPD (r=-0.66, P=0.05). Levels of HIV antibodies were positively correlated with both reservoir size (total-DNA, IPD, and IUPM) and activity (CA-RNA).
**Conclusion:** This TI trial found that smaller size and lower activity of the HIV reservoir predicted only a modest delay in HIV rebound for most participants, with the degree of association differing by early versus chronic ART initiation. However, the restricted reservoir size and activity in early-treated participants support previous reports that early ART may enrich for post-treatment control. We also identified key HIV-specific CD8 immune responses associated with smaller intact HIV reservoir size.

**380 DECAY KINETICS OF FREE VIRUS, INTACT & DEFECTIVE PROVIRUSES, & 2LTR CIRCLES ON ART**

**Jennifer A. White**[1], Francesco R. Simonetti[1], Subul Beg[1], Niklas Bachmann[1], Natalie McMyn[1], Weiwei Dai[1], William Ford[1], Jun Lai[1], Christina Bunch[1], Joyce Jones[1], Ruy M. Ribeiro[2], Alan S. Perelson[2], Janet Siliciano[1], Robert Siliciano[1]
[1]*The Johns Hopkins University School of Medicine, Baltimore, MD, USA,* [2]*Los Alamos National Laboratory, Los Alamos, NM, USA*

**Background:** A stable latent reservoir for HIV-1 in resting CD4+ T cells that persists despite antiretroviral therapy (ART) is a major barrier to cure. In persons living with HIV-1 (PLWH), levels of plasma HIV-1 RNA decay rapidly following initiation of ART. The decay is biphasic and reduces viremia to below the limit of detection of clinical assays. The first phase of decay reflects the short half-life of the majority of productively infected cells ($t_{1/2}$ = 1 day). The second phase represents the slower turnover of a second population of infected cells ($t_{1/2}$ = 14 days). It is presumed that these productively infected populations are CD4+ T cells, but their identity and the differences between the two populations have never been clear. These rapidly decaying populations do not become part of the stable latent reservoir which is comprised of resting CD4+ T cells with integrated intact HIV-1 DNA that have a much longer half-life and constitute the major barrier to cure.
**Methods:** We analyzed these time dependent decay processes in 17 PLWH initiating ART for the first time or after prolonged treatment interruption. Using the intact proviral DNA assay that distinguishes intact and defective proviruses, we measured the decay of HIV 1 in circulating CD4+ T cells.
**Results:** We found that circulating infected CD4+ T cells include few if any cells that decay with a half-life of 1 day. Instead, for the first three months of ART, most of the circulating CD4+ T cells with intact proviruses decay with a half-life on the order of weeks ($t_{1/2}$ = 13 days), slightly faster than the 2nd phase decay of plasma virus in the same participants ($t_{1/2}$ = 30 days). After the first three months of ART, the decay slope changes and CD4+ T cells with intact proviruses decay with a half-life of 19 months for the following nine months. Proviruses with defects at the 5′ or 3′ end of the genome show equivalent monophasic decay at rates that vary among individuals. 2LTR circles decay in a biphasic fashion paralleling intact proviruses, a finding that resolves previous controversy about their use as a marker for ongoing viral replication.
**Conclusion:** This study defines the in vivo decay rates of cells with intact and defective proviruses and 2LTR circles during the early period of ART suppression. Understanding these complex early decay processes is important for correct use of reservoir assays and may provide insights into properties of surviving cells that can constitute the stable latent reservoir.

**381 FORMATION OF THE LONG-LIVED EARLY RESERVOIR IS PUNCTUATED BY EPISODIC SEEDING**

**Olivia D. Council**[1], Melissa-Rose Abrahams[2], Sarah B. Joseph[1], Nigel Garrett[3], Matt Moeser[1], Ean Spielvogel[1], Amy Sondgeroth[1], Lynn Tyers[2], David Matten[2], Sergei L. Kosakovsky Pond[4], Nancie Archin[1], David M. Margolis[1], Salim S. Abdool Karim[3], Ronald Swanstrom[1], Carolyn Williamson[2]
[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC, USA,* [2]*University of Cape Town, Cape Town, South Africa,* [3]*Centre for the AIDS Programme of Research in South Africa, Durban, South Africa,* [4]*Temple University, Philadelphia, PA, USA*

**Background:** The majority of the long-lived reservoir is fixed around the time of ART initiation. However, a portion forms earlier in untreated infection and the kinetics of the establishment of this early-forming reservoir have not

been elucidated. Here, we examine the seeding of the early reservoir to better understand the forces driving its establishment.

**Methods:** Longitudinal pre-ART RNA sequences from four subgenomic regions of HIV-1 (3 in env and 1 in nef) were obtained through MiSeq with PrimerID for five women in the CAPRISA002 cohort over a median of 10 pre-ART time points (range: 7 – 14). After 5 yrs (average) of suppressive ART, PBMCs were collected and total DNA extracted. Proviral reservoir amplicons of the 3'half of the HIV-1 genome were generated at end-point dilution using nested PCR and sequenced using PacBio with barcodes. Neighbor-joining trees were constructed using all unique pre-ART RNA sequences and DNA reservoir sequences, after masking hypermutated positions in DNA sequences. Entry into the long-lived reservoir was estimated using the phylogenetic relationship between pre-ART RNA and reservoir sequences. A model for continuous seeding of the early reservoir was generated that assumed the probability a reservoir sequence would be seeded at any pre-ART time point was based solely on the length of time between a given time point and the next. The observed temporal distribution of reservoir sequences was then compared to this model of an early reservoir that is continuously seeded.

**Results:** A median of 100 unique proviral reservoir sequences were obtained for each participant (range: 46 – 133). All sequences dating to the year before ART were removed and subsequent analyses performed on the remaining unique, early-forming sequences (median of 46, range: 27 – 64). For 4 of 5 participants, the observed distribution of DNA reservoir sequences fell between one and two standard deviations above the median of the distribution generated by the continuous seeding model, and were also significant as episodic events when all data were pooled. In each case, there were clear pre-ART time points that contained significantly more reservoir sequences than expected under this model.

**Conclusion:** The low-level frequent seeding of the early reservoir is punctuated by episodic bursts of reservoir formation. Elucidating the forces that drive both frequent and episodic seeding of the early-forming reservoir will enable the design of interventions to block them, thus reducing the size of the reservoir.

**FIGURE:**

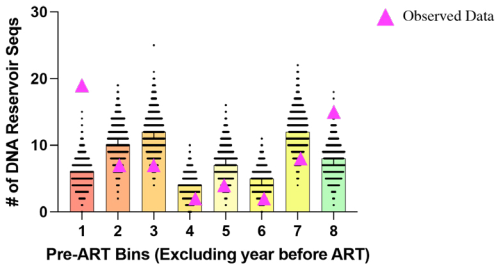



**Figure 1. Specific pre-ART time points are over-represented in the early-forming reservoir.** Black dots represent simulated entries of DNA sequences into the long-lived reservoir under a model of continuous formation. Pink triangles represent the actual number of DNA sequences observed entering the reservoir at each pre-ART time point.

## 382 MEASURING HIV-1 RESERVOIR DYNAMICS DURING LONG-TERM ANTIRETROVIRAL THERAPY

**Thuy Nguyen**[1], Mary E. Zipparo[1], Lindsey Adams[1], Shawn Hill[1], Matthew A. Adan[2], Erin Madeen[1], Chuen-Yen Lau[1], Frank Maldarelli[2]

*[1]National Cancer Institute, Frederick, MD, USA, [2]National Cancer Institute, Bethesda, MD, USA*

**Background:** Quantifying the HIV-1 reservoir is essential for development and evaluation of HIV-1 cure strategies. The intact proviral DNA assay (IPDA), which distinguishes intact from defective proviruses by analyzing the HIV packaging signal and env regions, indicates that intact proviruses decay more rapidly than defective proviruses in HIV-infected individuals on antiretroviral therapy (ART). IPDA does not measure HIV-1 LTR, so does not quantify all proviruses. To investigate the dynamics of total, intact, and defective proviruses during ART, we complimented the IPDA with a multiplexed assay that simultaneously quantifies HIV-1 LTR and gag.

**Methods:** Peripheral blood mononuclear cells (PBMC) were obtained from participants at pretherapy (n=10), and after short-(2-7 years on ART;n=9), intermediate-(8-15y; n=9), and long-(18-21y;n=8) term ART. Levels of LTR, gag (Anderson et al., 2020) and intact, defective provirus (IPDA) (Bruner et al.2018) were measured by droplet digital PCR. The HIV-1 DNA levels measured by the two assays were evaluated using correlation analyses.

**Results:** Prior to ART, median (IQR) HIV-1 viral RNA level was 5.04 (4.82-5.70) $\log_{10}$ copies/mL plasma and CD4 was 259 (183-395) cells/µl; median (IQR) of HIV-1 DNA LTR and gag levels were 3.41 (3.14-3.52) and 2.99 (2.66-3.06) $\log_{10}$ copies/1e6 PBMC. From pretherapy to short-, intermediate-, and long-term ART, LTR levels declined 2.2, 4.4, and 4.1-fold, while gag levels underwent greater decay (2.5, 6.6, and 7.3-fold, respectively). By IPDA, median (IQR) levels of intact, 3'-deleted/hypermutated, and 5'-deleted proviruses at pretherapy were 2.81 (2.56-3.18), 2.76 (2.43-2.87) and 2.72 (2.48-2.84) copies/1e6 PBMC, respectively. The level of intact proviruses declined 8.1, 19.5, and 44.3-fold. After long-term ART, the level of intact proviruses was below the limit of detection for four participants. The levels of HIV-1 DNA LTR, gag and intact, defective proviruses were significantly correlated (p-values <0.0001, rs= 0.39-0.97). The ratio of total DNA (IPDA)/intact was significantly correlated with LTR/gag (p=0.006, r =0.57) but higher than LTR/gag ratio, indicating substantial levels of gag persist during long term ART.

**Conclusion:** Total levels of HIV-1 DNA measured in the LTR/gag assay are highly correlated with IPDA, and still quantifiable during long-term ART when intact proviruses are below the limit of detection. LTR/gag complements IPDA to capture the dynamics of HIV-1 decay and useful where intact proviruses are not detected by IPDA.

## 383 HIV PROVIRUSES MIMIC THE CLONALITY OF HIGHLY EXPANDED CD4+ T CELLS IN PEOPLE ON ART

**Daniel B. Reeves**[1], Danielle N. Rigau[2], Francesco R. Simonetti[2], Hao Zhang[2], Leah H. Rubin[2], Stephen Gange[2], Nadia Roan[3], Phyllis Tien[3], Joseph B. Margolick[2], Frederick M. Hecht[3], Steven G. Deeks[3], Joshua Schiffer[1], Janet Siliciano[2], Robert Siliciano[2], Annukka A. Antar[2]

*[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]University of California San Francisco, San Francisco, CA, USA*

**Background:** During antiretroviral therapy (ART), a population of latently infected CD4+ T cells carrying HIV proviruses persists in people with HIV (PWH). These cells can clonally proliferate despite ART. The rank-abundance (clonality) distribution of infected cell clones is characterized by a few very large clones and many smaller clones. We hypothesized that this clonality distribution emerges naturally from the proliferative dynamics of CD4s.

**Methods:** We sequenced full genome HIV proviruses from resting CD4s (~100 per individual) and obtained rmCD4 TCR-β sequences (~105 per individual) from the same blood samples in 4 ART-suppressed individuals (3 men, 1 woman) at approximately 2 and 9 years after ART initiation. rmCD4 TCR sequences were also obtained from a sample approximately 1 year after ART initiation. Consistent viral load suppression was documented over 10 years of follow-up. We additionally sequenced rmCD4 TCRs in 4 age/sex/race-matched HIV-uninfected individuals at three similar timepoints. We quantitatively summarized clonality distribution by sample-size normalized ecological metrics including the slope of rank-abundance distributions.

**Results:** After 9 years on ART, the slope of rank abundance distributions differed between HIV infected cells and the general population of rmCD4s, with HIV-infected cells characterized by a significantly more uneven clonality distribution than rmCD4s. We found that a mathematical model of rmCD4 clonality distribution was more accurate if it allowed for two different slopes for the rank abundance distribution, one for the large (most highly-expanded clones, ~top 10-20 in rank) and one for the smaller clones (~>20 rank, Figure). The rank abundance slope of HIV-infected cells was significantly different from the small, but not the large rmCD4 TCR slope. This indicates that the HIV-infected cell clonality distribution mimics the subpopulation of highly expanded rmCD4s. Additional longitudinal analyses showed that in 3 time points over 8 years, highly-expanded rmCD4 clones persist in the peripheral circulation of both PWH on ART and HIV-uninfected individuals, though to a greater degree in HIV-uninfected individuals (p<0.02). Highly expanded clones from earlier time points were significantly likely to contract by later time points.

**Conclusion:** We observed similar clonality distributions in HIV-infected CD4 clones and highly expanded rmCD4+ T cell clones in peripheral circulation, suggesting they may be subject to similar proliferative forces.

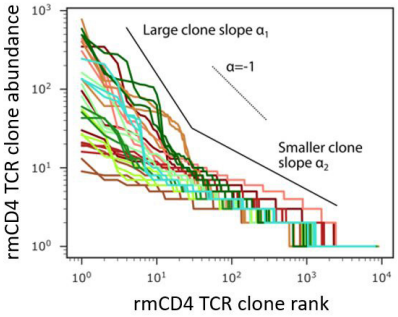



**Figure.** The abundance of resting memory (rm)CD4+ T cell clones in peripheral blood samples are plotted by rank order of highest abundance (1) to lowest abundance. Clones from people living with HIV on ART are pink, browns, and reds. Clones from age/sex/race-matched HIV-seronegative people are greens and blues.

## 384 PREDICTORS OF HIGH TOTAL AND INTACT HIV RESERVOIR AMONG CHILDREN WITH HIV IN KENYA

New Investigator Scholar

**Jillian Neary**[1], Carolyn S. Fish[2], Noah Cassidy[2], Dalton C. Wamalwa[3], Agnes Langat[4], Evelyn Ngugi[4], Sarah Benki-Nugent[1], Hellen Moraa[3], Barbra A. Richardson[1], Jennifer Slyker[1], Dara A. Lehman[2], Grace John-Stewart[1]
*[1]University of Washington, Seattle, WA, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]University of Nairobi, Nairobi, Kenya, [4]Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** Studies evaluating predictors of HIV reservoir size in children often solely quantify total reservoir. We determined predictors of total and intact viral reservoir size among children living with HIV.
**Methods:** Among children who initiated antiretroviral therapy (ART) at <1 year of age, HIV reservoir was quantified at multiple timepoints over 5 years post-ART among those virally suppressed (HIV RNA<1,000 copies/ml) within 6 months prior to and at reservoir assessment. Total and intact HIV DNA was quantified with a novel cross-subtype intact proviral DNA assay (CS-IPDA). Generalized estimating equation models with exchangeable correlation structure were used to determine predictors of reservoir size (continuous) or high reservoir (dichotomized: high cut-off for total reservoir ≥2 log c/ml and for intact reservoir ≥1 log c/ml). Quantitative PCR was used to measure cytomegalovirus (CMV) and Epstein-Barr virus (EBV) viral loads in plasma. All models adjusted for time on ART at reservoir measurement and age at ART initiation.
**Results:** Among 64 children with HIV reservoir assessed, median age at ART initiation was 4.7 months (IQR: 4.0, 7.2). Larger total HIV reservoir size was significantly associated with baseline: CD4%, HIV RNA level, and CMV level. Larger intact HIV reservoir size was associated with lower CD4% and higher HIV RNA level at baseline (Table 1). Each 1-log increase in pre-ART HIV RNA level was associated with a 40% higher intact reservoir level (95%CI=1.16, 1.70). Children on a protease inhibitor (PI)-based regimen were 31% more likely to have a higher intact reservoir than children on non-nucleoside reverse transcriptase inhibitors (NNRTI) (95%CI=1.03-1.67). Each 1-log increase in pre-ART CMV level was associated with a 20% higher intact HIV reservoir level (95%CI=1.05-1.36).
**Conclusion:** These data suggest that early HIV RNA levels, immunosuppression, and CMV-antigenic stimulation play a role in sustainment of the stable replication-competent intact HIV reservoir in children. Tolerability of PI-based regimens could explain the association with larger intact reservoir; however, mechanisms to explain this association should be further interrogated.

| | Log Total HIV Reservoir (continuous outcome log10[copies/million]) | | | Log Intact HIV Reservoir (continuous outcome log10[copies/million]) | | |
|---|---|---|---|---|---|---|
| | aRR* | 95% Confidence Intervals | p-value | aRR* | 95% Confidence Intervals | p-value |
| Male | 1.03 | (0.96, 1.11) | 0.363 | 1.11 | (0.86, 1.45) | 0.423 |
| Baseline CD4% (continuous) | 0.99 | (0.99, 1.00) | 0.001 | 0.98 | (0.96, 1.00) | 0.046 |
| Baseline HIV RNA ($log_{10}$[copies/ml]) | 1.12 | (1.07, 1.17) | <0.001 | 1.40 | (1.16, 1.70) | 0.001 |
| Baseline ART regimen contains PI (ref: NNRTI) | 1.05 | (0.98, 1.12) | 0.188 | 1.31 | (1.03, 1.67) | 0.028 |
| Baseline underweight (WAZ <-2) | 1.02 | (0.95, 1.10) | 0.531 | 1.08 | (0.82, 1.42) | 0.569 |
| Baseline stunting (HAZ<-2) | 1.05 | (0.98, 1.12) | 0.177 | 1.03 | (0.79, 1.33) | 0.850 |
| Baseline wasting (WHZ<-2) | 1.02 | (0.91, 1.15) | 0.739 | 1.09 | (0.71, 1.66) | 0.704 |
| Ever hospitalized at baseline | 1.07 | (0.97, 1.18) | 0.191 | 0.98 | (0.72, 1.32) | 0.881 |
| Baseline CMV log10 (copies/ml) | 1.04 | (1.00, 1.07) | 0.034 | 1.20 | (1.05, 1.36) | 0.006 |
| Baseline CMV viremic (>50 copies/ml) | 1.04 | (0.79, 1.37) | 0.755 | 3.25 | (0.51, 20.90) | 0.214 |
| Baseline EBV viremic (>50 copies/ml) | 1.01 | (0.92, 1.12) | 0.791 | 0.81 | (0.50, 1.31) | 0.390 |

*aRR: adjusted relative risk – conditioned on time since ART initiation and age at ART initiation in the model

## 385 VIRUSES WITH 5'-LEADER DELETIONS ARE A CAUSE OF NONSUPPRESSIBLE HIV-1 VIREMIA

**Francesco R. Simonetti**[1], Jennifer A. White[1], Saif Yasin[2], Joseph Varriale[1], Milica Moskovljevic[1], Jiayi Duan[1], Kyle Rhodehouse[1], Andrei Gheorghe[3], Alison L. Hill[1], Hao Zhang[1], Christin [2], Christopher Hoffmann[1], Michael Summers[2], Janet Siliciano[1], Robert Siliciano[1]
*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]University of Maryland, Baltimore County, Baltimore, MD, USA, [3]Harvard University, Cambridge, MA, USA*

**Background:** Expanded populations of HIV-1-infected CD4+ clones are an established cause of nonsuppressible viremia (NSV). Prior work showed that these clones can carry replication-competent proviruses that represent a small fraction of all infected cells. Although defective proviruses comprise 90% of infected cells and retain viral transcription, it is unclear whether they can gain clinical relevance and complicate ART management.
**Methods:** We characterized the source of NSV from 2 individuals on ART by single genome sequencing from plasma virions and CD4+ T cells, qVOA, and full genome sequencing paired to integration site analysis. We tested the impact of 5' Leader (5'L) deletions in an NL4-3 virus backbone. 5'L RNA dimerization and NC binding were assessed in vitro. RNA from specific proviruses was measured by probing the sequence across the deletion. We quantified proviral abundance by LTR and integration-site-specific duplex digital PCR in longitudinal samples and CD4+ T cell subsets.
**Results:** Both study participants had NSV for >4 years with a median of 80 and 115 cps/mL, and no response to ART intensification. In participant 1, an HLA-B57+ viremic controller with small reservoir (<0.06 IUPM), a single provirus was responsible for 100% of viremia, represented 50% of all env+ proviruses, and was integrated in the ADK gene. Participant 2 showed a large reservoir (15 IUPM) and an oligoclonal population of viruses in plasma (10 variants). The second largest plasma clone (13%) represented 6% of proviral sequences and was inserted in DNAJB14. Both proviruses had intact ORFs and small 5'L deletions (22 and 21nt) surrounding the MSD site. 5'L RNA analyses demonstrate more labile dimerization and partially reduced NC binding. T cell activation ex vivo shows that these proviruses are inducible, use a novel spicing donor, and their gRNA can be packaged. However, viral particles are not infectious due to lack of Env incorporation. Finally, we show that ADKd22 rapidly expanded around the onset of NSV, reached a plateau of 50 cps/10^6 CD4+ T cells (17% of all proviruses), and is siloed in effector memory cells.
**Conclusion:** Our study shows that 5'L-defective proviruses can cause NSV. The peculiar position of the deletion and the extensive proliferation of these clones result in sufficient viral production to cause persistently detectable but replication-incompetent viremia. The long-term clinical consequences as well as the specific drivers of the proliferation and expression of these clones remain unknown.

## 386 INTACT HIV TRANSCRIPTS ARE RARE IN ART-SUPPRESSED INDIVIDUALS

New Investigator Scholar

**Holly A. Martin**[1], Gayatri Nikhila Kadiyala[1], Sushama Telwatte[1], Adam Wedrychowski[1], Tsui-Hua Chen[2], Sara Moron-Lopez[1], Rebecca Hoh[1], Steven G. Deeks[1], Joseph K. Wong[1], Steven A. Yukl[1]
*[1]University of California San Francisco, San Francisco, CA, USA, [2]San Francisco VA Medical Center, San Francisco, CA, USA*

**Background:** Genetically intact proviruses are the source of viral rebound after ATI. However, it is unclear to what degree intact viral RNA is expressed in ART-suppressed people with HIV (PWH).
**Methods:** To address this question, we developed and validated a novel "intact viral RNA assay" (IVRA) that applies primers/probes from the IPDA (for the commonly mutated Psi and RRE regions) to single HIV RNA molecules in droplets (by dd-RT-PCR) to quantify HIV RNA molecules that are likely "intact" (Psi+RRE+) vs.3'defective (Psi+RRE-) or 5'defective (Psi-RRE+). The IPDA and IVRA were applied to DNA and RNA from 4-11 replicate aliquots of 3e5-1e6 CD4+T cells isolated from the blood of 10 ART-suppressed PWH.
**Results:** Intact HIV DNA was detected in 9/10 individuals, while intact HIV RNA was detected in 6/10 (vs. 9/10 for defective HIV RNA). Levels of 3' defective HIV DNA (median[range]=145 [51-844] copies/1e6 CD4+T cells, or 42% [21-78%] of all proviruses) were not significantly different from 5' defective HIV DNA (193 [50-1388] copies/1e6 cells, or 52% [16-77%] of all proviruses) and were higher than intact HIV DNA (10.6 [0-206] copies/1e6 cells, or 3.9% [0-10%] of proviruses; P<0.01). In contrast, levels of 3' defective HIV RNA (84.6 [0-251]

copies/1e6 cells, or 94% [75-99%] of all HIV RNA) were higher than 5' defective HIV RNA (1.7 [0-16] copies/1e6 cells, or 5.5% [0.8-15%] of HIV RNA; P<0.01) or intact HIV RNA (1.1 [0-19] copies/1e6 cells, or 0.7% [0-19%] of HIV RNA; P<0.01). These differences persisted when each HIV RNA type was normalized to its corresponding HIV DNA. By limiting dilution analysis, the frequency of CD4+T cells with 3' defective HIV RNA (1.1e-6 [0 to >8e-6]) was greater than the frequency with 5'defective HIV RNA (4.9e-7 [0 to >8e-6]; P<0.05) or intact HIV RNA (1.6e-7 [0 to 6.1e-7]; P<0.05). Using ratios of HIV RNA+ cell frequencies to HIV DNA, we calculated that a median of 0.023% [0-0.14%] of all proviruses and 0.25% [0-2.9%] of intact proviruses transcribe intact HIV RNA.

**Conclusion:** The vast excess of 3' defective over 5' defective or intact HIV RNA, which was not observed in the HIV DNA, likely represents a block to HIV transcriptional completion. A very small proportion of all HIV RNA is intact, and a very low proportion of proviruses or even intact proviruses transcribe intact HIV RNA. This intact HIV RNA likely contributes to immune activation/inflammation on ART and may be a major source of viral rebound after ART interruption.

## 387 EARLY ANTIRETROVIRAL THERAPY REDUCES BUT DOES NOT ELIMINATE HIV DNA IN BLOOD

**Trevor A. Crowell**[1], Justin Ritz[2], Lu Zheng[2], Asma Naqvi[3], Joshua Cyktor[3], Scott F. Sieg[4], Javier R. Lama[5], James F. Rooney[6], Lawrence Fox[7], Jintanat Ananworanich[8], Joseph J. Eron[9], Gert Van Zyl[10], John W. Mellors[3], Eric S. Daar[11]
*[1]US Military HIV Research Program, Silver Spring, MD, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Case Western Reserve University, Cleveland, OH, USA, [5]Asociacion Civil Impacta Salud y Educacion, Lima, Peru, [6]Gilead Sciences, Inc, Foster City, CA, USA, [7]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [8]University of Amsterdam, Amsterdam, Netherlands, [9]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [10]Stellenbosch University, Cape Town, South Africa, [11]Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA, USA*

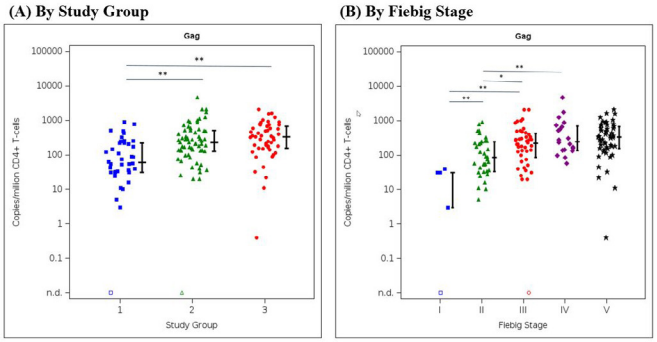
**Background:** Antiretroviral therapy (ART) initiated during acute or early HIV infection (AEHI) may limit HIV reservoir formation and facilitate HIV remission. We evaluated HIV DNA levels in blood at and after suppressive ART initiation across AEHI stages in a multinational study.

**Methods:** ACTG 5354 enrolled adults with AEHI at 30 sites in the Americas, Africa, and Southeast Asia. Participants initiated ART during AEHI, either with a study-provided integrase inhibitor-based regimen or another prescribed regimen. Fiebig stage at ART initiation was retroactively assigned by centralized testing and categorized per protocol as Group 1 (Fiebig I/II), Group 2 (Fiebig III/IV) or Group 3 (Fiebig V). The primary study endpoint was undetectable HIV DNA at week 48 of ART in 5 million purified CD4+ T cells by sensitive qPCR assays targeting HIV gag and pol. To assess HIV-specific immune responses, peripheral blood mononuclear cells were stimulated with potential T cell epitope peptide pools and stained for expression of CD3, CD4 and CD8 and intracellular interferon-gamma.

**Results:** From January 2017 to December 2019, 188 participants initiated ART during Fiebig stages I (n=6), II (n=43), III (n=56), IV (n=23), and V (n=60). Median age was 27 years (interquartile range 23-38), 27 (14%) were female, and 96% cisgender. Fiebig I participants had lower pre-ART HIV gag DNA than participants in all other Fiebig stages (all p<0.05) and trended toward lower pre-ART HIV pol DNA as well (all p<0.10). Among 153 participants with HIV RNA <50 copies/mL without protocol-defined ART interruption, 100% had detectable HIV gag or pol DNA at 48 weeks of ART with negative intra-assay controls. Participants who started ART during the earliest Groups and Fiebig stages had significantly lower HIV gag and pol DNA levels at 48 weeks (all trend tests p<0.001, Figure). Week 48 HIV DNA did not correlate with CD4+ or CD8+ T cell interferon-gamma responses to env, gag, nef, or pol peptide stimulation (rho range -0.10 to +0.14, all p>0.05).

**Conclusion:** ART initiation in earlier stages of AEHI reduced but did not eliminate the persistence of HIV-infected cells in blood. In contrast to prior studies, sensitive and specific qPCR assays performed on a large number of CD4+ T cells detected HIV DNA in all participants after 48 weeks of ART regardless of Fiebig stage at ART initiation. These findings may explain why rapid viral rebound has been observed after ART cessation in early-treated individuals with undetectable HIV DNA by less sensitive methods.

**Figure. HIV DNA at 48 Weeks after Antiretroviral Therapy Initiation**




HIV DNA was measured in 5 million purified CD4+ T cells. Undetectable HIV DNA measurements are indicated with open symbols. Two participants with undetectable HIV DNA by qPCR for *gag* at 48 weeks (1 in Fiebig I, 1 in Fiebig III; open symbols) were detectable by qPCR for *pol* (data not shown). Bars represent medians and interquartile ranges. Pairwise comparisons were done by Wilcoxon test (* < 0.05; ** < 0.01).

## 388 INTACT NONINDUCIBLE PROVIRUSES ARE GENERATED DURING ACUTE HIV AND CAN PERSIST ON ART

**Pierre Gantner**[1], Supranee Buranapraditkun[2], Caroline Dufour[1], Amélie Pagliuzza[3], Corentin Richard[3], Rémi Fromentin[3], Julie Mitchell[4], Eugene Kroon[5], Suteeraporn Pinyakorn[6], Merlin Robb[6], Nittaya Phanuphak[5], Denise C. Hsu[6], Sandhya Vasan[6], Lydie Trautmann[4], Nicolas Chomont[1]
*[1]Université de Montréal, Montreal, Canada, [2]Chulalongkorn University, Bangkok, Thailand, [3]Centre de Recherche du CHUM, Montreal, Canada, [4]Oregon Health and Sciences University, Portland, OR, USA, [5]SEARCH, Bangkok, Thailand, [6]US Military HIV Research Program, Silver Spring, MD, USA*

**Background:** HIV reservoirs are established during acute infection and persist during ART. However, the intactness and inducibility of these viral genomes remain poorly characterized. Here, we obtained near-full length HIV genome sequences of rare non inducible proviruses detected during acute infection and followed their fate during ART.

**Methods:** We collected longitudinal blood samples (pre-ART and after 96 weeks of ART) from 6 participants with acute HIV (AH, n=2 individuals/Fiebig stage [II, III and IV/V]) and 2 participants with chronic HIV (CH) enrolled in the RV254/RV304 studies (Bangkok, Thailand). We measured cell-associated viral transcripts (LTR-gag and Tat-Rev) as well as the frequency of HIV-DNA harbouring cells and capsid protein p24 expressing cells (HIV-Flow) with or without stimulation (PMA/ionomycin) pre- and post-ART. Cells harbouring non-induced proviruses (p24-) were sorted for near-full length HIV genome sequencing at both time points.

**Results:** Before ART, productively infected cells (p24+) displayed a memory phenotype (92%) and expressed low levels of HLA Class I when compared to uninfected cells. The frequency of p24+ cells and the levels of cell-associated LTR-gag or Tat-Rev HIV-RNAs did not significantly increase upon stimulation, suggesting that reactivable proviruses were rare during acute infection. After 96 weeks of ART, none of the participants who initiated ART during AH displayed detectable p24+ cells (in contrast to CH), which was consistent with low to undetectable levels of cell-associated HIV transcripts even after stimulation. However, total and integrated HIV-DNA were readily detected in p24- cells from the majority of the participants both pre- and post-ART. The analysis of 223 proviral sequences retrieved from p24- cells pre-ART revealed that 28% of the non-inducible proviruses were intact. This proportion dropped to 11% after 96 weeks of ART, which was attributed to the accumulation of defects in the ψ, Rev, Env and RRE regions (p<0.05). Clonally expanded proviral sequences were observed in 6/8 participants, including intact non-induced proviruses that persisted on ART in two AH participants.

**Conclusion:** Collectively, these data indicate that a pool of latently-infected cells harbouring intact HIV proviruses that are refractory to in vitro latency reversal is established early during acute infection and can persist during ART.

## 389 EXPRESSION OF HIV-1 ANTISENSE TRANSCRIPTS IN DONORS ON ART

New Investigator Scholar

**Basic** Science:

**Rachel Sklutuis**[1], Jennifer L. Groebner[1], Valerie F. Boltz[1], Wei Shao[2], Rui Li[3], Steven G. Deeks[4], Brandon Keele[2], Fabio Romerio[3], Mary F. Kearney[1]
*[1]National Cancer Institute, Frederick, MD, USA, [2]Frederick National Laboratory for Cancer Research, Frederick, MD, USA, [3]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [4]University of California San Francisco, San Francisco, CA, USA*

**Background:** Natural antisense transcripts (NATs) are a class of RNA molecules transcribed from the opposite strand of a protein-coding gene to regulate gene expression. NATs encoded by viruses, such as Hbz in HTLV-1, have been shown to regulate viral expression. In HIV-1 M group, in vitro experiments have shown that expression of a NAT called Ast (nt6888-9461 in HXB2) promotes the establishment and maintenance of latency through PRC2-induced epigenetic regulation of viral expression. We investigated levels of Ast expression in single infected cells isolated from donors on ART.
**Methods:** PBMCs were obtained from 4 donors in the SCOPE cohort on suppressive ART for a median of 5.5 years (4-19 years) and from 1 donor reinitiating ART following a recent treatment interruption. The samples were tested using the cell-associated RNA and DNA single-genome sequencing (CARD-SGS) assay adapted to measure the fraction of infected cells with Ast RNA spanning nt7497-9237 (nt numbers correspond to HXB2). Antisense RNA in two regions of gag and pol (nt764-2283 and nt1826-3529) were also evaluated. Additionally, a digital PCR approach was used to examine both sense and antisense expression in the region spanning 7497nt-7565nt.
**Results:** A median of ~5% of infected PBMCs contained the 1.7kb fragment of Ast RNA measured by CARD-SGS. Levels of expression ranged from 1-30 copies per cell. The shorter fragment of Ast RNA within the same region measured using the strand-specific digital RT-PCR approach was detected in a median of 28% of infected PBMCs. Antisense RNA in gag and pol regions was also detected in 4% and 11% of infected cells, respectively when measured by CARD-SGS. A similar fraction of infected cells contained sense env and pol RNA as antisense Ast RNA in most donor samples.
**Conclusion:** Our findings confirm expression of HIV-1 Ast RNA in donors on ART and indicate that antisense transcripts may span the entire length of the HIV-1 provirus, consistent with in vitro studies. Detection of Ast RNA in unstimulated cells from donors on ART warrants the investigation of its bifunctional role as a coding and a regulatory RNA in vivo. Altering in vivo levels of Ast may represent a new HIV-specific approach to reverse or induce viral latency.

## 390 EVALUATION OF GLIAL HIV RESERVOIRS USING A HUMANIZED BLOOD AND BRAIN MOUSE

**Saumi Mathews**[1], Edward Makarov[1], Lili Guo[1], Li Wu[1], Larisa Y. Poluektova[1], Santhi Gorantla[1]
[1]*University of Nebraska Medical Center, Omaha, NE, USA*

**Background:** Understanding glial cells, microglia/astrocytes, the main targets of HIV infection and initiators of HIV-associated neurocognitive disorders (HAND) pathology, remains elusive due to the lack of small animal models for HIV-1 brain infection. A novel humanized mouse reconstituted with human hematolymphoid system and brain glia is developed to facilitate studies on HIV brain infection, glial reservoirs, and neuropathology. Human glia from infected mice were analyzed at a single-cell level to reveal cellular mechanisms of HIV glial infection.
**Methods:** Human interleukin-34 transgenic-NOG pups were transplanted with autologous human neural progenitor cells and hematopoietic stem cells. At 20 weeks, mice were infected with HIV-1ADA, and at 12 weeks post-infection, human glia were isolated using human HLA-ABC magnetic beads from infected and uninfected brains for single-cell RNA sequencing using 10X genomics. Reads were aligned to human and HIV reference genomes and analyzed with Partek Genomics Suite. Differential gene expression ($p<0.05$) from HIV positive, HIV exposed, and naive cells were identified. Affected pathways and networks were determined using Ingenuity pathway analysis.
**Results:** New humanized mouse has all HIV target cells: the human immune system, microglia, and astrocytes, as confirmed by flow cytometry and immunohistology. Analysis of human cells from HIV-1 infected and uninfected mouse brains by scRNAseq yielded 11837 individual cells identifying 13022 genes. Clustering of cells from infected and uninfected mice identified 15 distinct cell clusters. Each sample group, infected and uninfected, clustered differently, indicating a unique genetic profile. We identified 1028 cells harboring complete HIV or HIV-specific genes in these clusters. Cells harboring whole HIV genome showed significant expression of genes such as EGR1, LGALS1, CDKN1A, ATF3, MDM2, PPP1R15A in comparison to HIV exposed cells. Cellular pathway analysis indicated differential interferon signaling, PTEN signaling, and hypercyto/chemokinemia suggestive of active immune reaction in response to infection.
**Conclusion:** Humanized astrocyte-microglia mice allow to assess molecular and functional signatures of different microglial and astrocyte populations, including the HIV reservoir cells, during combination antiretroviral therapy, and generate single cell-based atlas to reveal associations with the HIV-neuropathology and therapeutic targets for viral reservoir eradication.

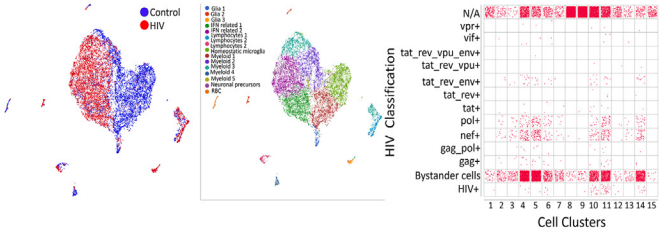



Figure 1 **Cluster identification of human glia with HIV-1 infected cells.** (A) UMAP plot showing cells from HIV-1 infected (red) and uninfected (blue) mice clustered distinctively. (B) UMAP plot showing clustering of cells identified based on gene signature as glial, neuronal precursors and myeloid clusters (C) A total of 1028 cells which contain HIV-1 specific gene regions such as *gag, pol, nef, vif, tat, vpr and tat_rev_vpu_env* were identified.

## 391 ALTERED MICROGLIAL GENOME STRUCTURE AND TRANSCRIPTION IN HIVE IMPACT HIV INTEGRATION

New Investigator Scholar

**Amara Plaza-Jennings**[1], Brandon Pratt[2], Benjamin K. Chen[1], Lotje De Witte[1], Susan Morgello[1], Hyejung Won[2], Schahram Akbarian[1]
[1]*Icahn School of Medicine at Mt Sinai, New York, NY, USA,* [2]*University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

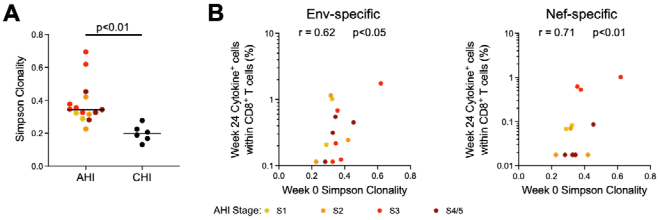
**Background:** HIV infection of microglia in the central nervous system can lead to HIV associated neurocognitive disorder (HAND) and contributes to the formation of a potentially large reservoir, but the mechanisms of these processes remain poorly understood. Patients undergo an initial viremia prior to being placed on antiretroviral therapy, thus it is important to understand how active viremia impacts microglia and contributes to HAND and reservoir seeding. Here we perform studies of primary human microglia in the setting of HIV encephalitis (HIVE) to understand how active viremia alters microglial transcription, 3D-genome architecture, and viral integration.
**Methods:** Postmortem frontal cortex samples from the Manhattan HIV Brain Bank were used for all studies. Bulk isolated nuclei were submitted for 10X Chromium single nucleus RNA-sequencing (snRNA-seq; n=2 HIV-, n=3 HIV+ without HIVE [HIV+], and n=3 HIV+ with HIVE [HIVE]). In situ Hi-C was performed on fixed Irf8+ microglial nuclei sorted using fluorescence activated nuclei sorting (FANS; n=2 HIV-, n=2 HIVE). Integration site analysis was performed on FANS isolated NeuN+ neuronal and NeuN- non-neuronal nuclei for a total of 27 samples (n= 6 HIV-, n= 15 HIV+, n= 6 HIVE).
**Results:** HIVE microglia undergo restructuring of 3D chromatin architecture of >6% of the genome when compared to HIV- microglia. Regions that switch to a more open conformation relate to the immune response while regions that enter a more closed conformation relate to cell adhesion and synapses. Regions that switched to a more open conformation had higher gene expression in HIVE microglia as compared to HIV- by snRNA-seq. HIVE microglia overall show increased expression of microglial activation and immune markers, driven by a subset of microglia that are actively transcribing HIV. Viral integration sites were found in highly expressed microglia genes and >75% were in regions of open chromatin defined by Hi-C. Furthermore, integration sites were enriched in regions that underwent changes in transcription, chromatin compartment, and cis-chromosomal 3D contacts.
**Conclusion:** These findings link HIVE to changes in microglial gene expression and spatial genome organization that influence viral integration. These cell-type specific maps of 3D-genome architecture, transcription, and integration in HIVE provide important insights as to how HIV infection impacts microglial function and contributes to disease development and viral persistence. Funded by R61DA048207, R01DA054526, and U24MH10093

## 392 COMPARTMENTALIZED CLONAL EXPANSIONS OF CD8+ T CELLS IN CSF DURING ACUTE HIV INFECTION

**Julie Mitchell**[1], Caroline Subra[2], A Julian Pacheco Mendez[1], Faria Fatmi[2], Blake Colton[1], Supranee Buranapraditkun[3], Suteeraporn Pinyakorn[2], Carlo Sacdalan[4], Somporn Tipsuk[4], Nittaya Phanuphak[4], Denise C. Hsu[2], Sandhya Vasan[2], Serena S. Spudich[5], Lydie Trautmann[1]
[1]*Oregon Health and Sciences University, Portland, OR, USA,* [2]*US Military HIV Research Program, Silver Spring, MD, USA,* [3]*Chulalongkorn University, Bangkok, Thailand,* [4]*Institute of HIV Research and Innovation, Bangkok, Thailand,* [5]*Yale University, New Haven, CT, USA*

**Background:** Activated CD8+ T cells infiltrate the central nervous system (CNS) early in acute HIV infection (AHI). Whether CD8+ T cells in cerebral spinal fluid (CSF) are CNS specific or recirculate from the peripheral blood is not yet known. We characterized the CD8+ T cells in CSF and blood in different HIV infection stages by sequencing their T cell receptor (TCR) and measuring frequencies of HIV-specific CD8+ T cells.
**Methods:** Participants enrolled in the Thai RV254/RV304 cohorts who consented to optional lumbar puncture were studied. Blood and CSF samples were collected at the time of ART initiation during AHI (n=15) or chronic HIV infection (CHI; n=6), as well as after 24 and 96 weeks of ART in both groups. Genomic DNA was purified from polyclonally expanded CD8+ T cells for sequencing of the TCRβ chain. Repertoire clonality was measured by Simpson clonality index and diversity by Morisita index. HIV-specificity was measured in polyclonally expanded CD8+ T cells by cytokine staining after stimulation with CRF01_AE HIV peptide pools.
**Results:** Comparison of the CD8+ TCRβ repertoires between CSF and blood revealed differences prior to ART intiation in AHI (p=0.07), but not in CHI or after ART, suggesting CNS compartmentalization of CD8+ T cells in AHI. CD8+ TCRβ repertoires were significantly more clonal in AHI than in CHI in CSF (Fig. 1A, p<0.001), but not in blood. CD8+ T cell turnover in CSF, measured as change in TCRβ diversity between pre-ART and 24 weeks post-ART, was higher in participants who initiated ART in AHI compared to CHI (p=0.06). HIV-specific CD8+ T cells were detectable in the CSF in all stages of AHI and were still detected at similar frequencies on ART in contrast to blood where they declined after ART. Interestingly, the level of TCRβ clonality in CSF during AHI was associated with the frequencies of Env-specific (r=0.62, p<0.05), Nef-specific (r=0.71, p<0.01), Pol-specific (r=0.63, p<0.05), and Rev/Tat-specific (r=0.59, p<0.05) CD8+ T cells in the CSF detected after 24 weeks of ART (Fig. 1B). There were no correlations between TCRβ clonality and HIV-specific CD8+ T cell responses in the peripheral blood.
**Conclusion:** These data suggest that there is compartmentalization of CD8+ T cells in the CSF during AHI that is not seen after ART intiation or in CHI. Further, increased clonal expansion of CD8+ T cells in AHI, probably driven by local expansion of HIV-specific CD8+ T cell responses, were associated with persistence of HIV-specific CD8+ T cell responses in the CNS after ART.

**Figure 1. Increased clonality of CD8⁺ T cells in the CSF during acute HIV infection correlated with HIV-specific responses after ART.**




## 393 SIV-INFECTED CD4+ T CELLS CARRY VIRUS TO THE BRAIN

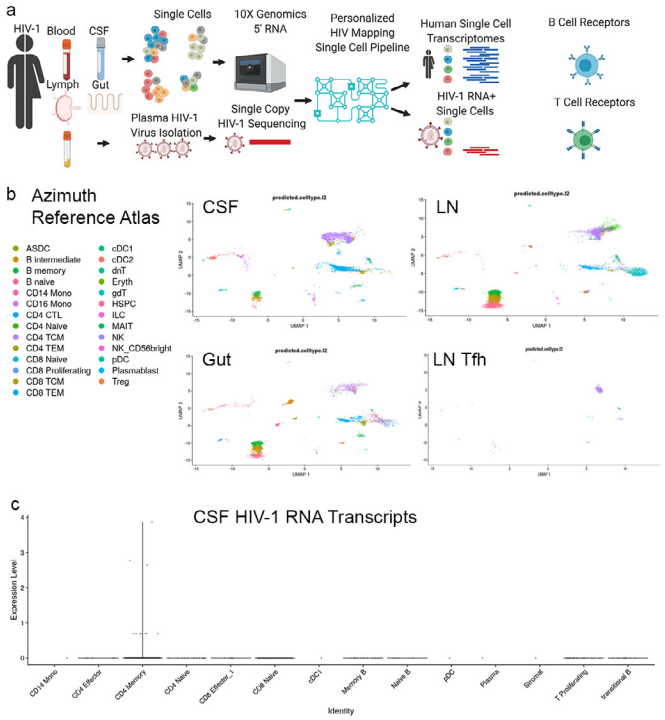
**Howard S. Fox**[1], Brenda M. Morsey[1], Meng Niu[1], Katy Emanuel[1], Benjamin G. Lamberty[1], Andrew J. Trease[1]
*[1]University of Nebraska Medical Center, Omaha, NE, USA*

**Background:** The brain is infected early in HIV and SIV infection. Since virus can be found within cells of the myeloid lineage (microglia and macrophages) in the brain, many presume that infected myeloid cells (monocytes) in the blood carry infection to the brain. Understanding the mechanisms by which the brain reservoir is initiated, maintained, and possibly replenished are critical for strategies to protect the brain from damage and efforts towards an HIV cure. We hypothesized that by examining the blood and brain cells of monkeys during acute infection we could identify the cell type carrying SIV into the brain.
**Methods:** Three male rhesus monkeys were inoculated intravenously with SIVmac251, one animal served as an uninfected control. On day 12 p.i. animals were necropsied, with intravascular perfusion to clear blood-borne cells. CD11b+ monocytes and CD4+ T cells were FACS-purified from the blood. CD11b+ and/or CD45+ (macrophages, microglia, and lymphocytes) were FACS-purified from enriched brain cell preparations. 8,000 cells each from both blood preparations, and 24,000 cells from the brain preparation, were processed for single-cell RNA sequencing (scRNA-seq) from each animal. Sequences were aligned to a custom rhesus+SIV genome. Bioinformatic analysis included dimensionality reduction, graph-based clustering, and marker gene assignment; statistical analysis was performed by ANOVA with step-up false discovery rate correction.
**Results:** 3.67% of blood CD4+ T cells, <0.01% of blood monocytes, and 0.15% of brain myeloid and lymphoid cells expressed SIV RNA. The infected blood CD4+ T cells were present in two populations, distinguishable by their transcriptomes including reciprocal expression of RNA for the cytotoxic molecule granzyme B (GZMB) and the transcription factor TCF-1 (TCF7). In the brain, only the GZMB+TCF7- population of SIV-infected CD4+ T cells were found, in addition to infected cells characteristic of microglia. Flow cytometry confirmed the presence of GZMB+ CD4+ T cells in the brains of infected monkeys.
**Conclusion:** CD4+ T cells are infected with SIV in both the blood and the brain during the acute infection period. Cells similar to the infected CD4+ T cells in the brain were present in the blood. The transcriptome of these cells, as revealed by scRNA-seq, resembles that of cytotoxic lymphocytes. The trafficking of these unconventional CD4+ T cells to the brain represents an important new aspect of neuroHIV pathogenesis and contributes to a barrier to HIV cure.

## 394 MULTI-COMPARTMENT FRESH SINGLE-CELL STUDIES IN AN INTERNATIONAL HIV RESEARCH SETTING

**Michael J. Corley**[1], Supranee Buranapraditkun[2], Panadda Sawangsinth[3], Alexandra Schuetz[4], Sodsai Tovanabutra[5], Alina Pang[1], Shelli F. Farhadian[6], Nittaya Phanuphak[3], Carlo Sacdalan[3], Denise C. Hsu[7], Sandhya Vasan[7], Serena S. Spudich[6], Lishomwa Ndhlovu[1]
*[1]Weill Cornell Medicine, New York, NY, USA, [2]Chulalongkorn University, Bangkok, Thailand, [3]SEARCH, Bangkok, Thailand, [4]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [5]Walter Reed Army Institute of Research, Silver Spring, MD, USA, [6]Yale University, New Haven, CT, USA, [7]Henry M Jackson Foundation, Bethesda, MD, USA*

**Background:** Single cell.methods have enhanced the resolution at which cells in blood and tissues can be studied in people with HIV (PWH). Yet, capturing the native multi-omics state of cells obtained from multiple tissue compartments and from rare and vulnerable cells in cerebrospinal fluid (CSF) while avoiding artifacts that may arise from cryopreservation remains a challenge for single cell studies, more so in resource limited settings.
**Methods:** To demonstrate single cell studies of fresh cells from PWH are logistically feasible in a resource limited setting, we built upon the opportunities of the RV254/SEARCH010 and RV304/SEARCH013 studies enrolling people with acute and chronic HIV (AHI & CHI) in Bangkok, Thailand where uptake of optional procedures including leukapheresis, lumbar puncture (LP), gut biopsy, and lymph node (LN) biopsy is high. Fresh cells were isolated from gut and LN, CSF, and blood over 2 days from an ART naïve PWH with CHI (Participant 1, Figure 1A), and from gut and blood from a PWH on suppressive ART initiated during AHI (Participant 2). The 10X genomics platform was used locally to generate single cell transcriptome and T-cell/B-cell receptor data from fresh specimens within hours of sampling. Seurat suite was used for analysis.
**Results:** Multi-omics single cell data was obtained for 28,400 freshly isolated lymph node cells, 5,968 gut cells, and 5,614 CSF cells from Participant 1 (Figure 1B). We also leveraged flow cytometry cell sorting capabilities of fresh T follicular helper cells from LN for multi-omics single cell profiling of 5,712 cells. In addition, multi-omics profiling was performed on 8,876 blood and 6,488 gut cells obtained on the same day from Participant 2. To enhance detection of HIV viral transcripts in the CHI ART naïve participant, we generated an individualized near full-length patched viral sequence to align sequencing reads and detected HIV transcript containing cells in all compartments with heterogenous single cells either producing high or low HIV transcripts. Notably, all HIV transcript containing cells in the CSF were identified in inferred CD4 memory T cells (Figure 1C).
**Conclusion:** We demonstrate the logistical feasibility of generating single cell multi-omics data from fresh cells from blood, CSF, LN, and gut in PWH in Bangkok. A personalized HIV mapping approach can be used to pinpoint infected single cells in tissue compartments including the CNS. This will enable cross-compartmental multi-omics studies to further interrogate HIV reservoirs.




## 395 PHARMACOGENETICS OF THE LATE-ONSET EFAVIRENZ NEUROTOXICITY SYNDROME (LENS)

**Roland van Rensburg**[1], Sam Nightingale[2], Naeem Brey[1], Christine H. Albertyn[1], Tracy Kellermann[1], Jantjie J. Taljaard[1], Tonya M. Esterhuizen[1], Phumla Sinxadi[2], Eric Decloedt[1]

*[1]Stellenbosch University, Cape Town, South Africa, [2]University of Cape Town, Cape Town, South Africa*

**Background:** Early-onset neuropsychiatric adverse effects of efavirenz are common and usually mild. The recently-described late-onset efavirenz neurotoxicity syndrome (LENS) presents as severe ataxia and/or encephalopathy, and is associated with supratherapeutic efavirenz plasma concentrations (>4 µg/mL). Efavirenz is primarily metabolized by cytochrome P450 2B6 (CYP2B6), with CYP2A6 as an accessory pathway. We hypothesized that participants with LENS would predominantly be CYP2B6 slow metabolizers. The aim of our study was to determine frequencies of CYP2B6 slow metabolizers and characterize plasma exposure of efavirenz and its primary metabolite, 8-hydroxyefavirenz, in participants with LENS.

**Methods:** Adult HIV-positive participants on efavirenz-based antiretroviral therapy presenting with LENS were prospectively enrolled into a descriptive case series. Genetic polymorphisms known to be associated with increased efavirenz plasma concentrations in CYP2B6 (rs3745274, rs28399499, rs4803419) and CYP2A6 (rs28399433) were selected, and used to determine proportions of slow metabolizers. We also genotyped selected NAT2 polymorphisms (rs1208, rs1799930, rs1799931, rs1801279, rs1801280) known to be associated with increased isoniazid concentrations, a known and common CYP2A6 enzyme inhibitor. Pharmacokinetic analyses were performed using liquid chromatography-tandem mass spectrometry. Median (IQR) efavirenz and 8-hydroxyefavirenz plasma concentrations were described.

**Results:** Fifteen participants were enrolled. Thirteen were Black-African, and 13 were female. Median weight was 49.9 kg with a median duration on efavirenz of 2.2 years. All 15 participants were successfully genotyped as slow CYP2B6 metabolizers, with six participants additionally having CYP2A6 heterozygous genotype. Thirteen were receiving isoniazid, and all 15 were genotypic NAT2 slow or intermediate acetylators. Efavirenz plasma concentration was markedly increased at 50.5 (47.0 to 65.4) µg/mL; 8-hydroxyefavirenz concentration was markedly decreased at 0.10 (0.07 to 0.15) µg/mL.

**Conclusion:** Our study is the largest prospective LENS series to date, and provides the first definitive evidence that LENS is associated with CYP2B6 slow metabolizer genotype, with a median efavirenz plasma concentration >12-fold higher than the defined upper limit of the therapeutic range. Isoniazid, NAT2 acetylator status, and low body weight are important contributors to LENS development.

## 396 CORRELATIONS OF UNDETECTABLE HIV DNA 96 WEEKS AFTER ART INITIATION DURING ACUTE HIV

**Gunn Pungpapong**[1], Phillip Chan[2], Denise C. Hsu[3], Carlo Sacdalan[2], Somchai Sreepleanjan[2], Peeriya Prueksakaew[2], Suteeraporn Pinyakorn[3], Bohyung Yoon[3], Sandhya Vasan[4], Sodsai Tovanabutra[4], Nittaya Phanuphak[2], Robert Paul[5], Nicolas Chomont[6], Serena S. Spudich[7]

*[1]Imperial College London, London, UK, [2]SEARCH, Bangkok, Thailand, [3]US Military HIV Research Program, Silver Spring, MD, USA, [4]US Military HIV Research Program, Bethesda, MD, USA, [5]University of Missouri St Louis, St Louis, MO, USA, [6]Université de Montréal, Montreal, Canada, [7]Yale University, New Haven, CT, USA*

**Background:** In chronic HIV, a larger HIV reservoir as measured by HIV DNA in PBMCs associates with worse cognition. We evaluated whether HIV DNA measured in PBMCs 96 weeks (wks) after ART started in acute HIV infection (AHI) associates with neuropsychiatric outcomes and examined pre-ART predictors of HIV DNA in PBMC at 96 wks.

**Methods:** RV254 cohort participants in Thailand initiated ART within 4 (IQR 3-5) days after AHI diagnosis and underwent neuropsychiatric (NP) assessment and blood sampling pre-ART (baseline, BL) and during follow-up. NP assessments included Patient Health Questionnaire-9 (PHQ-9) for depressive symptoms and a 4-test cognitive battery including Color Trails 1 and 2, Trail Making A and non-dominant hand grooved pegboard. Demographically adjusted Z-scores of the 4 tests were averaged to generate a composite NPZ-4 score. Total HIV DNA in PBMCs was measured by ultrasensitive LTR-gag real-time PCR at BL, wks 24, 48 and 96. Multivariable logistic regression determined factors that correlated with undetectable HIV DNA at wk 96.

**Results:** 124 RV254 participants had HIV DNA measurements at wk 96. 118 (95%) were male, with a median age 26. 59 (48%) presented at Fiebig stage I-II. At BL, median blood HIV RNA and HIV DNA levels were 5.6 (IQR 5-6.5) $log_{10}$ cps/ml and 186 (IQR 21.5-775.5) cps/$10_6$ PBMCs, respectively. Median CD4+ and CD8+ T-cell counts were 373 (IQR 278-529) and 482 (IQR 255-784) cells/mm3. The proportion of participants with detectable HIV DNA decreased from 100% at wk 0 to 70% (66/94), 67% (62/93) and 52% (45/87) at wks 24, 48 and 96, respectively. At wk 96, median HIV DNA was 4 (IQR 0-20) cps/$10_6$ PBMCs. NPZ-4 and PHQ-9 scores at wk 96 were statistically similar between those with detectable and undetectable HIV DNA. BL factors associated with undetectable HIV DNA at wk 96 include early Fiebig stage I-II (OR 2.8, p=0.024), lower plasma HIV RNA (OR 4.69, p=0.013), and higher CD4/CD8 ratio (OR 2.86, p=0.024). Multivariable analysis revealed that lower BL plasma HIV RNA (OR 4.67, p=0.016) and higher BL CD4/CD8 ratio (OR 2.84, p=0.031) remained independently associated with higher likelihood of undetectable HIV DNA at wk 96 (Table).

**Conclusion:** Though half of individuals had undetectable HIV DNA in PBMCs 96 wks after ART initiated during AHI, this finding did not associate with neuropsychiatric outcomes. Predictors of undetectable HIV DNA in PBMC included lower pre-ART plasma HIV-1 RNA and higher CD4/CD8 ratio, confirming that early events impact the HIV reservoir trajectory.

**Table. Factors Associated with Undetectable PBMC HIV DNA 96 weeks after ART Initiation during Acute HIV**

| | Odds ratio (95%CI) | p-value | Adjusted Odds ratio (95%CI) | p-value |
|---|---|---|---|---|
| **Age** | 1.01 (0.95 - 1.07) | 0.74 | | |
| **Gender** | | | | |
| Female | 6.00 (0.67 – 53.79) | 0.109 | | |
| Male | **Ref.** | | | |
| **Fiebig stage** | | | | |
| I-II | 2.80 (1.15 – 6.85) | 0.024 | | |
| III-IV | **Ref.** | | | |
| **HIV RNA at week 0** | | | | |
| <= 5 log 10 copies/mL | 4.69 (1.38 – 15.95) | 0.013 | 4.67 (1.10 – 7.34) | 0.016 |
| > 5 log 10 copies/mL | **Ref.** | | **Ref.** | |
| **Total HIV DNA at week 0** | | | | |
| Detectable | **Ref.** | | | |
| Undetectable | 10.5 (1.25 - 88.28) | 0.03 | | |
| **CD4 T cells at week 0** | | | | |
| CD4 <= 350 cells/mm$^3$ | **Ref.** | | | |
| CD4 > 350 cells/mm$^3$ | 2.18 (0.89 - 5.31) | 0.088 | | |
| **CD8 T cells at week 0** | | | | |
| CD8 <=500 cells/mm$^3$ | 1.54 (0.62 – 3.81) | 0.352 | | |
| CD8 > 500 cells/mm$^3$ | **Ref.** | | | |
| **CD4/CD8 ratio at week 0** | | | | |
| <= 1 | **Ref.** | | **Ref.** | |
| >1 | 2.86 (1.15 - 7.1) | 0.024 | 2.84 (1.10 - 7.34) | 0.031 |
| **ART regimen** | | | | |
| HAART | 1.69 (0.71 – 4.04) | 0.238 | | |
| MegaHAART | **Ref.** | | | |

## 397 EFFECT OF ART TREATMENT ON MACROPHAGE ACCUMULATION IN THE CNS WITH SIV

**Zoey K. Wallis**[1], Cecily Midkiff[2], Xavier Alverez[2], Kevin S. White[1], Patrick Autissier[1], Addison Q. Amadeck[1], Soon Ok Kim[1], Cinar Sumer[1], Yiwei Wang[1], Maia Jakubowski[1], Andrew Miller[3], Kenneth Williams[1]
*[1]Boston College, Chestnut Hill, MA, USA, [2]Tulane National Primate Research Center, Covington, LA, USA, [3]Cornell University, Ithaca, NY, USA*

**Background:** During HIV or SIV infection, the CNS acts as a viral reservoir that can rebound after ART interruption. Perivascular macrophages (PVMs) could be a major source of viral reseeding in the CNS. Utilizing a novel method of labeling CNS PVMs via SPION injection into the cerebrospinal fluid, we analyzed the trafficking and retention of SPION labeled macrophage to better understand the implications on cellular migration and draining lymphatics.
**Methods:** Thirteen SIV-infected, CD8-depleted Rhesus macaques received intracisternal SPION injection at early and late infection time-points (6 were untreated, 3 received antiretroviral therapy (ART) treatment, and 4 had ART treatment interrupted). 5-bromo-2'-deoxyuridine (BrdU) was administered intravenously and flow cytometry was performed on whole blood to detect recently emigrated monocytes from bone marrow. Plasma sCD163 measured by ELISA and plasma viral load was quantified. SPION containing cells were detected by immunofluorescence, Prussian blue staining, and macrophage accumulation was assessed in cortical regions and expressed as SPION containing cells/mm2. Prism was used for all statical analysis: Mann-Whitney t-test, Kruskal-Wallis test, and Spearman's rank test.
**Results:** The parenchyma of untreated SIV-infected macaques had the greatest number of SPION containing macrophage (4.5-fold change) compared to ART treated and ART interrupted macaques. There was a diminished effect of ART on the number of SPION containing cells in the meninges (Figure 1A). Monocyte turnover was significantly positively correlated with the accumulation of SPION containing cells in the brain parenchyma ($p<0.05$) and there was a trend of a positive correlation in the meninges (Figure 1B). There is a significant difference of macrophage accumulation in the CNS parenchyma between untreated and treated SIV-infection ($p<0.0005$) which positively correlates with the number of SPION containing macrophage in the parenchyma (Figure 1C). Triple label IHC was used to demonstrate Prussian blue SPION containing cells that are CD163 PVM adjacent to GLUT-1 positive CNS endothelial cells (Figure 1D).
**Conclusion:** There is a higher number of SPION labelled PVM in SIV-infected, non-ART treated animals than animals with ART treatment, indicating treatment results in less PVM accumulation and retention. Such treatment correlates with monocyte turnover, suggesting differential trafficking and retention of CD163+ macrophages in the parenchyma versus the meninges.

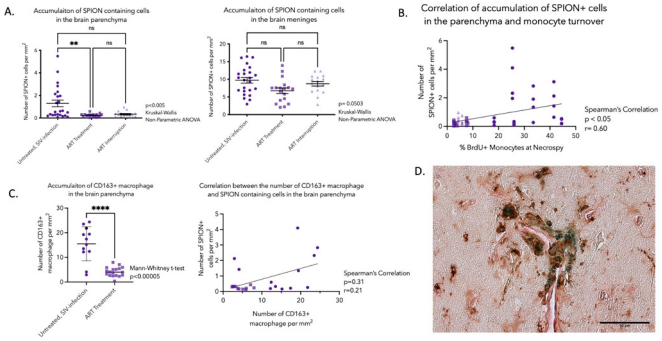



Figure 1. Accumulation of SPION labeled perivascular macrophage with SIV infection and ART treatment.

A. Analysis of Prussian blue staining for SPION containing macrophage identifies differences in the accumulation in the parenchyma and meninges. B. There is a significant positive correlation with increased monocyte turnover [detected from the percentage of BrdU+ monocytes] and the accumulation of SPION containing cells in the brain parenchyma ($p<0.05$). C. Accumulation of CD163+ perivascular macrophage is significantly decreased with ART treatment ($p<0.05$). There is a trend of positive correlation in the number of SPION containing macrophage and number of CD163+ PVM in the parenchyma. D. Triple label IHC was used assess localization of SPIONs (blue) to CD163+ macrophage (DAB: brown) near vasculature (GLUT-1: red). Image obtained using a 40x objective.

## 398 EFAVIRENZ PLASMA LEVELS, COGNITION, AND CENTRAL NERVOUS SYSTEM SIDE EFFECTS

**Alice Ranzani**[1], Francesco Castelli[2], Antonio Di Biagio[3], Antonella D'Arminio Monforte[4], Antonio D'Avolio[5], Alessandro Soria[1], Francesca Bai[6], Emanuele Focà[2], Lucia Taramasso[7], Andrea Calcagno[5], Paolo Bonfanti[8], Giuseppe Lapadula[8]
*[1]San Gerardo Hospital, Monza, Italy, [2]University of Brescia, Brescia, Italy, [3]University of Genoa, Genoa, Italy, [4]University of Milan, Milan, Italy, [5]University of Turin, Turin, Italy, [6]San Paolo Hospital, Milan, Italy, [7]San Martino Hospital, Genoa, Italy, [8]University of Milano–Bicocca, Milan, Italy*

**Background:** Efavirenz (EFV) plasma concentration (Cp) has been associated with central nervous system (CNS) side-effects; in vitro data suggest neurotoxicity may be mediated by 8-hydroxy(OH)-EFV. Whether EFV or 8-OH-EFV Cp are associated with neurocognitive (NC) impairment is debated.
**Methods:** Morning EFV and 8-OH-EFV Cp were measured by HPLC on frozen plasma samples collected during the screening of a randomized trial evaluating NC function after switching from EFV to rilpivirine (Swear Study). All participants (Pt) were on stable (>6 months) effective therapy with tenofovir/emtricitabine/EFV at bedtime. Pt underwent comprehensive NC assessment, evaluation of depression, anxiety, quality of sleep, CNS symptoms, self-reported Cognitive Failures (CFQ). Pt with altered findings repeated the tests 24 weeks after switching away from EFV. EFV and 8-OH-EFV Cp were compared using Mann-Whitney test according to impairment in the different assessments. Correlations between drug Cp and scores (baseline & 24-week changes) were explored with Spearman's test.
**Results:** Of 104 Pt, 87% males, 35% with high education, median age was 46.5 years (IQR 40-54). Median EFV and 8-OH-EFV Cp were 3108 (IQR 2559-3946) and 184 (IQR 118–289) ng/ml. EFV and 8-OH-EFV Cp did not significantly differ in Pt with or without asymptomatic NC impairment, although higher EFV Cp were observed in Pt with impaired executive function and language (table 1). Conversely, Pt with more CNS side-effects, high CFQ score, depressive symptoms and low-quality sleep had higher 8-OH-EFV (but not EFV) Cp. A trend to a weak correlation between EFV Cp and lower executive function ($R=-0.18$; $P=0.059$), motor function ($R=-0.19$; $P=0.054$), attention ($R=-0.17$; $P=0.082$) and language ($R=-0.17$; $P=0.093$) z-scores was found. Conversely 8-OH-EFV Cp was correlated with higher CNS symptom score ($R=0.26$; $p=0.007$), CFQ score ($R=0.18$; $P=0.066$) and PSQI score ($R=0.22$; $p=0.021$). Among 66 Pt switching away from EFV, baseline EFV Cp was not associated with changes in NC scores after 24 weeks whereas Pt with high 8-OH-EFV Cp (≥184 ng/ml) were more likely to experience CNS symptom improvement (CNS symptom score -8[-11 to -1] vs -1[-5 to 2]; $P<0.001$).
**Conclusion:** Higher 8-OH-EFV Cp is associated with CNS side effects. Such marker can be useful to identify Pt who can benefit the most from EFV discontinuation. EFV-but not 8-OH-EFV- Cp were marginally associated with NC performances, suggesting possible different pathways in determining detrimental effects on cognitive function.

**Table 1. Efavirenz and 8-hydroxy-efavirenz plasma levels in patients with and without selected clinical conditions (N=104)**

| | EFV plasma level Median (IQR), ng/ml | p value | 8-OH-EFV plasma level Median (IQR), ng/ml | P value |
|---|---|---|---|---|
| **Asymptomatic neurocognitive impairment (ANI)** | | | | |
| Yes (N=21) | 3425 (2825-3837) | 0.471 | 239 (116-354) | 0.627 |
| No (N=83) | 3090 (2378-3979) | | 180 (119-278) | |
| **Memory/Recall impairment** | | | | |
| Yes (N=31) | 3103 (2495-3897) | 0.776 | 185 (116-367) | 0.680 |
| No (N=73) | 3114 (2586-3979) | | 182 (119-272) | |
| **Executive function impairment** | | | | |
| Yes (N=9) | 4719 (2926-4949) | 0.055 | 222 (91-367) | 0.865 |
| No (N=94) | 3058 (2495-3849) | | 181 (118-283) | |
| **Attention impairment** | | | | |
| Yes (N=14) | 2915 (2148-4949) | 0.733 | 132 (91-261) | 0.209 |
| No (N=89) | 3114 (2618-3897) | | 186 (120-299) | |
| **Motor function impairment** | | | | |
| Yes (N=27) | 3425 (2515-3849) | 0.689 | 214 (112-299) | 0.675 |
| No (N=77) | 3026 (2586-3979) | | 171 (120-278) | |
| **Language impairment** | | | | |
| Yes (N=7) | 4949 (3102-7154) | 0.021 | 239 (91-480) | 0.632 |
| No (N=96) | 3022 (2505-3873) | | 181 (118-289) | |
| **Depression (BDI-II >90th percentile)** | | | | |
| Yes (N=23) | 3311 (2292-3913) | 0.906 | 247 (162-367) | 0.067 |
| No (N=81) | 3102 (2586-3979) | | 164 (109-272) | |
| **Anxiety (BAI >90th percentile)** | | | | |
| Yes (N=14) | 3585 (2617-4313) | 0.438 | 214 (132-299) | 0.389 |
| No (N=90) | 3023 (2531-3897) | | 181 (112-287) | |
| **Sleep impairment (PSQI >5)** | | | | |
| Yes (N=35) | 2985 (2292-3897) | 0.397 | 222 (132-355) | 0.078 |
| No (N=69) | 3246 (2736-4086) | | 171 (112-268) | |
| **CNS Symptom Score ≥6** | | | | |
| Yes (N=55) | 3205 (2618-3849) | 0.948 | 222 (132-341) | 0.027 |
| No (N=49) | 3090 (2531-4547) | | 151 (107-264) | |
| **CFQ score ≥9** | | | | |
| Yes (N=52) | 3258 (2556-3817) | 0.971 | 218 (128-339) | 0.078 |
| No (N=52) | 3025 (2559-4490) | | 152 (103-273) | |

Asymptomatic neurocognitive impairment was defined as z-scores below -1 in ≥2 cognitive domains. Single domain impairment was defined as a z-score below -1.

List of abbreviation: BAI, Beck's Anxiety Index; BDI, Beck's Depression Index; CFQ, Cognitive Failure Questionnaire; CNS, Central Nervous System; PSQI, Pittsburgh Sleep Quality Index.

## 399 REVERSIBILITY OF CENTRAL NERVOUS SYSTEM ADVERSE EVENTS IN COURSE OF ART

**Lucia Taramasso**[1], Giancarlo Orofino[2], Elena D. Ricci[3], Barbara Menzaghi[4], Giuseppe V. De Socio[5], Nicola Squillace[6], Giordano Madeddu[7], Francesca Vichi[8], Benedetto M. Celesia[9], Chiara Molteni[10], Filippo Del Puente[11], Eleonora Sarchi[12], Goffredo Angioni[13], Antonio Cascio[14], Paolo Bonfanti[15]
*[1]IRCCS AOU San Martino-IST, Genoa, Italy, [2]Amedeo di Savoia Hospital, Torino, Italy, [3]Asia Foundation, Milan, Italy, [4]ASST della Valle Olona, Busto Arsizio, Italy, [5]Santa Maria della Misericordia General Hospital, Perugia, Italy, [6]San Gerardo Hospital, Monza, Italy, [7]University of Sassari, Sassari, Italy, [8]Santa Maria Annunziata Hospital, Florence, Italy, [9]Garibaldi Hospital, Catania, Italy, [10]Alessandro Manzoni Hospital, Lecco, Italy, [11]University of Genoa, Genoa, Italy, [12]SS. Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy, [13]SS Trinità Hospital, Cgliari, Italy, [14]University Hospital of Palermo, Palerno, Italy, [15]University of Milano–Bicocca, Milan, Italy*

**Background:** Central nervous system (CNS) adverse events (AE) can occur during various antiretroviral therapies (ART), as well as being a major cause of treatment discontinuation during dolutegravir-containing ART (DTG). The purpose of this study is to evaluate the frequency of SNC-AE in DTG- and non-DTG containing ART and their reversibility one year after ART change.

**Methods:** Observational prospective SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals) cohort. Factors associated with CNS-AE were estimated using a Cox proportional-hazards model. Rate of AE occurrence and resolution were compared between DTG and non-DTG ART.

**Results:** 4751 people living with HIV (PLWH) were enrolled in DTG (N=1138) and non-DTG (N=3613) cohorts. Sixty SNC-AE leading to ART discontinuation were reported, 26/3613 (0.7%) in non DTG-cohorts (2/731 lopinavir, 1/616 atazanavir, 2/721 darunavir, 8/421 rilpivirine, 5/514 raltegravir, 3/339 elvitegravir and 5/211 bictegravir), and 34/1138 (3.1%) in DTG-cohort. Survival analysis in strata of DTG and non-DTG-based regimens showed a significantly higher rate of discontinuations due to CNS-AE in DTG (logrank p<0.0001), with a longer time between drug initiation and SNC-AE in DTG than non-DTG group, 10.0 (IQR 4-15) versus 4.0 (IQR 1-7) months (p=0.0160). PLWH naïve to ART, with higher CD4-T cell count and with psychiatric disorder were those more likely to develop a SNC-AE (Table). The risk of SNC-AE was lower in PLWH who did not receive DTG after adjusting for potential confounders (adjusted Hazard Ratio 0.34, 95% confidence interval 0.20-0.59, p=0.0001). After drug discontinuation, follow up was available for 52/60 PLWH. In non-DTG cohorts the event was considered resolved in 18/19 cases, while, in DTG, AE resolution was reported in 30/33 cases. The four cases in which the event did not resolve were all switched to an INSTI-containing ART, associated to NNRTI in one case. The probability of AE reversibility was not different in DTG and non-DTG cohorts, nor based on sex, age, ethnicity, or CDC stage (p>0.1 for all), with a trend toward lower rate of AE resolution in PLWH with psychiatric disorder (p= 0.0770) and in those switched to INSTI after the AE (p=0.0168).

**Conclusion:** AE leading to ART discontinuation were more frequent in DTG than non-DTG treated PLWH. However, most AE resolved after ART switch, with similar frequency in DTG and non-DTG cohorts.

**Table.** Crude and adjusted hazard ratio (HR) for discontinuation due to central nervous system events.

| Variable | Crude HR | 95% CI | P | Adjusted HR* | 95% CI | P |
|---|---|---|---|---|---|---|
| Sex F (ref. M) | 1.35 | 0.79-2.31 | 0.27 | | | |
| Age (by 1 year) | 1.02 | 1.00-1.04 | 0.054 | | | |
| Age (ref. <50 years) | **2.03** | **1.22-2.39** | **0.007** | 1.57 | 0.91-2.69 | 0.10 |
| Weight (by 5 Kgs) | 1.00 | 0.92-1.10 | 0.94 | | | |
| Ethnicity (ref. Caucasian) | 1.16 | 0.46-2.89 | 0.75 | | | |
| Hepatitis C virus (ref. HCV-Ab negative) | | | | | | |
| HCV-Ab+ | 1.13 | 0.66-1.93 | 0.66 | | | |
| Naïve (ref. experienced) | **2.02** | **1.15-3.55** | **0.01** | **2.25** | **1.22-4.13** | **0.009** |
| CDC stage (ref. A) | | | | | | |
| B | 0.93 | 0.51-1.68 | 0.80 | | | |
| C | 0.78 | 0.41-1.46 | 0.43 | | | |
| CD4 (ref. <250) | | | | | | |
| 250-499 | 1.38 | 0.66-2.86 | 0.39 | 1.37 | 0.66-2.86 | |
| 500-749 | 1.36 | 0.60-3.08 | 0.46 | 1.16 | 0.50-2.68 | |
| ≥750 | **2.70** | **1.31-5.58** | **0.007** | **2.22** | **1.03-4.79** | **0.04** |
| Previous CNS disorders* | **2.69** | **1.32-5.46** | **0.006** | **2.46** | **1.20-5.06** | **0.01** |
| Cohort (ref. DTG) | | | | | | |
| no DTG | **0.26** | **0.16-0.43** | **<0.0001** | **0.34** | **0.20-0.59** | **0.0001** |

*depression, anxiety, psychosis, bipolar disorder

## 400 IMPACT OF INTEGRASE STRAND TRANSFER INHIBITORS ON COGNITION IN THE HAILO COHORT

**Jane O'Halloran**[1], Charles Goss[1], Mansi Agarwal[1], Sarah Cooley[1], Kunling Wu[2], Rachel Presti[1], Beau M. Ances[1], Katherine Tassiopoulos[2], Kristine Erlandson[3]
*[1]Washington University in St Louis, St Louis, MO, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University of Colorado Denver, Denver, CO, USA*

**Background:** Understanding the impact of antiretroviral therapy (ART) on neuropsychological (NP) outcomes, particularly cognition, in aging people with HIV (PWH) is important. Integrase strand transfer inhibitors (InSTIs) have previously been associated with poorer cognitive outcomes.

**Methods:** From ACTG's observational aging cohort study A5322 (HAILO), we identified PWH who had 1) switched to an INSTI 2) had at least two NP assessments prior to and one after switch, 3) and maintained viral suppression throughout the follow up period on InSTI. Prior to HAILO enrollment, participants were followed in ACTGs A5000 (ALLRT) cohort and this data was included. NP performance was assessed by NPZ4 (z-scores [normed raw scores] averaged for Trail making A [TMA] and B [TMB], Digit Symbol [DSY] and Hopkins Verbal Learning Test [HVLT-R]). Scores were adjusted for sex, race, age, education and learning effects. Changes in cognitive outcomes from the pre-switch (initial NP tests to InSTI switch) and post switch (InSTI switch to end of follow up) periods were estimated using piecewise linear mixed models.

**Results:** Data from 395 PWH, including 5,824 NP assessments were included. Mean age at switch was 54 years, 81% were male sex, gender not available. 51% were white non-Hispanic, 29% Black non-Hispanic, and 20% Hispanic. Average observation time was 9 years pre- and 3 years post-switch. Mean z-scores at 9 years pre switch, InSTI switch and 3 years post switch are in Table 1. NPZ4 scores increased significantly pre- and post- switch but there was no significant difference in slopes between time periods (pre 0.036/year [95% CI 0.03, 0.043]; post 0.022/year [0.006, 0.005]; p=0.147). Each NP component test increased pre-switch (all p<0.01). Post-switch, TMA and DSY continued to increase (all p<0.01), but there were no differences in the rate of change pre-switch compared to post-switch (all p>0.05). HVLT-R had a non-significant decrease post-switch (p=0.22), resulting in a negative impact on the slope compared to pre-switch (p=0.03).

**Conclusion:** In this cohort, NP assessment scores increased over time; however, the overall mean change in NPZ4 was less than half a standard deviation and not clinically significant. HVLT-R, an assessment of memory, did have a small, but statistically significant change post switch to InSTI. Further research is required to determine if the domain specific changes identified are clinically relevant, but overall, InSTIs do not have a clear or consistent detrimental effect on NP outcomes.

**Table 1. Predicted mean z scores at time of switch to INSTI and average follow-up time pre/post switch.**

| | NPZ4 | HVLT-R | TMA | TMB | DYS |
|---|---|---|---|---|---|
| Time point in study | Mean (95% CI) | Mean (95% CI) | Mean (95% CI) | Mean (95% CI) | Mean (95% CI) |
| 9 years pre-switch | -0.148 (-0.239, -0.057) | -0.717 (-0.825, -0.608) | -0.384 (-0.485, -0.283) | -0.182 (-0.284, -0.08) | 0.386 (0.263, 0.508) |
| Switch to INSTI | 0.177 (0.079, 0.275) | -0.525 (-0.638, -0.412) | 0.217 (0.101, 0.333) | 0.353 (0.236, 0.47) | 0.689 (0.558, 0.82) |
| 3 years post-switch | 0.243 (0.141, 0.346) | -0.581 (-0.705, -0.456) | 0.336 (0.214, 0.458) | 0.402 (0.273, 0.531) | 0.818 (0.682, 0.955) |

*9 years pre-switch and 3 years post-switch corresponds to the average follow-up time pre/post switch.

## 401 HIV-1 Nef IMPAIRS MYELIN AND DISRUPTS GLIAL CELLS IN THE CENTRAL NERVOUS SYSTEM

**Jessica K. Schenck**[1], Michael I. Bukrinsky[1], Robert H. Miller[1]
*[1]George Washington University, Washington, DC, USA*

**Background:** HIV-associated neurocognitive disorder (HAND) pathogenesis has been linked to white matter damage, but the mechanisms underlying HIV-associated demyelination are unclear. We have previously shown that HIV-1 Nef is secreted from cells in extracellular vesicles (EVs) and impairs cholesterol efflux from macrophages via the cholesterol transporter ABCA1. Since oligodendrocytes require cholesterol for myelination, this study examined the effects of Nef EVs on glial cells, myelin structure, and ABCA1 expression in the central nervous system (CNS).

**Methods:** EVs carrying recombinant Nef were produced by transfected HEK293T cells and applied to mouse spinal cords in vivo, mouse cerebellar slice cultures ex vivo, and mixed mouse cortical cultures in vitro. EVs produced by

cells transfected with an empty vector served as control. Myelin and glial cells were stained for immunohistochemistry and quantified via ImageJ. ABCA1 protein expression was assessed by capillary electrophoresis. Between group differences were assessed via two-tailed t-tests.

**Results:** Mouse spinal cords injected with Nef EVs showed a 9% decrease in the proportion of myelin basic protein (MBP) immunoreactivity compared with controls (p=0.1596), consistent with focal myelin lesions. Supporting this, Nef-treated cerebellar slice cultures showed a significant 48% decrease in MBP immunoreactivity compared to controls (p=0.0117). Nef-injected spinal cords also displayed a significant 42% decrease in the proportion of GFAP+ astrocytes (p=0.0405) and 33% increase in the proportion of IBA1+ microglia (p=0.3005) compared with controls, indicating altered microglia and astrocyte infiltration. Treating mixed cortical cultures with Nef EVs resulted in a significant 45% decrease in the proportion of O4+ cells compared with controls (p<0.0001), indicating disruption to mature pre-myelinating oligodendrocytes in vitro. Nef-induced morphological disruptions of these cells in vitro were also observed, including decreased branch number and complexity. Capillary electrophoresis analysis of cell lysate from dissociated mouse cortical cultures treated with Nef EVs showed a significant 31% reduction in ABCA1 protein expression compared to controls (p=0.0200).

**Conclusion:** Together, these data suggest that Nef perturbs myelin integrity in the CNS, disrupts glial cells, and alters ABCA1 expression in cortical cells. Further work will examine the role of Nef-mediated myelin impairment in HIV-associated cognitive deficits.

## 402 NLRP3 INFLAMMASOME SIGNALING PATHWAY IS UPREGULATED IN BRAINS OF PEOPLE WITH HIV-1

New Investigator Scholar

**Alice K. Min**[1], Amara Plaza-Jennings[1], Susan Morgello[1], Schahram Akbarian[1], Talia H. Swartz[1]
[1]*Icahn School of Medicine at Mt Sinai, New York, NY, USA*

**Background:** Human immunodeficiency virus type 1 (HIV-1) causes a chronic disease that may be associated with neuroinflammation. In the setting of neuroinflammation, people with HIV-1 (PWH) can develop cognitive impairment: with active brain viral replication, this reflects HIV encephalitis (HIVE); in the absence of replicating HIV, mechanisms underlying brain inflammation despite viral suppression on antiretroviral therapies (ART) are unclear. One hypothesis is that HIV-1 latent reservoir in the brain give rise to chronic inflammation and cognitive impairment. The molecular mechanisms of this neuroinflammation have not been well characterized and the data for HIV-1 latency in the central nervous system are lacking. Here, we present data from single nuclei RNA transcriptome sequencing analyses on post-mortem brains of PWH.

**Methods:** Using 10x Genomics Chromium platform, we performed high-throughput single nucleus RNA sequencing (snRNA-seq) on post-mortem frontal cortex brain tissue of three different groups: 1) control subjects (n=2), 2) PWH without HIVE (-HIVE, n=3), 3) PWH with HIVE (+HIVE, n=3). The -HIVE group had an average CD4 T lymphocyte count of 516 and viral load (VL) of 440. The +HIVE group had an average CD4 T lymphocyte count of 11 and VL of 623,068.

**Results:** HIV transcript level was significantly elevated in a subset of microglia in post-mortem brains of PWH +HIVE, but not in post-mortem brains of PWH -HIVE. In PWH +HIVE, HIV transcripts represented the top 0.3% of the most highly expressed transcript in the microglial transcriptome. The brain's lymphoid compartment also expressed HIV, but its level was lower compared to the microglia, in the top 0.7% of the overall lymphoid transcriptome. More microglial cells expressed HIV transcript and the average level of expression exceeded the lymphocytes. In addition, there was elevated transcription of pro-inflammatory signaling genes in the PWH compared to their matched controls. These genes included the purinergic receptors, NLRP3 inflammasome signaling components, and pro-inflammatory cytokines.

**Conclusion:** We found that the purinergic receptors and NLRP3 inflammasome signaling genes are more highly expressed in the brains of PWH compared to their matched controls. We also found that HIV is very highly expressed in the microglia of PWH +HIVE, but not in PWH -HIVE. Hence, we propose that differential expression of pro-inflammatory signaling genes in the microglia could play a role in HIV-associated neuroinflammation and development of HIVE.

## 403 CONCOMITANT CARDIAC PATHOLOGY WITH ENCEPHALITIS IN SIV-INFECTED ANIMALS WITH AIDS

**Kevin S. White**[1], Joshua A. Walker[1], Patrick Autissier[1], Andrew Miller[2], Qingsheng Li[3], Rachel Burrack[3], Woong-Ki Kim[4], Kenneth Williams[1]
[1]*Boston College, Chestnut Hill, MA, USA,* [2]*Cornell University, Ithaca, NY, USA,* [3]*University of Nebraska–Lincoln, Lincoln, NE, USA,* [4]*Eastern Virginia Medical School, Norfolk, VA, USA*

**Background:** Cardiac disease (CVD) and cognitive disorder are the most common comorbidities of PLWH despite antiretroviral therapy (ART). Monocyte activation and macrophage accumulation in the heart and the CNS occur with cardiac pathology or SIV encephalitis (SIVE) indicating the two may be mechanistically linked. We asked if SIV-infected macaques with AIDS co-develop CVD and SIVE and studied monocyte/macrophages in the pathogenesis of their occurrence.

**Methods:** 23 SIV-infected, CD8+ lymphocyte-depleted, macaques with AIDS were grouped by cardiac fibrosis, inflammation, myocyte degeneration, and SIVE, and the prevalence and severity of CVD and SIVE together compared to animals with CVD or SIVE only, and animals with no significant findings (NSF) and no SIVE (SIVnoE). Numbers of cardiac macrophages, collagen deposition, SIV-infection, CD14+CD16+ monocytes and plasma virus, galectins-3 and -9, sCD163, and IL-18 were assessed.

**Results:** Of 23 animals with AIDS, 10 had CVD and SIVE (43.5%), 6 had CVD only or SIVE only (26.1%), and 7 had NSF and SIVnoE (30.4%). 16 animals had AIDS with comorbidities; 10 (62.5%) had CVD and SIVE, and 6 (37.5%) had CVD or SIVE only. CVD and SIVE animals had increased cardiac CD163+ (2.7X), CD206+ (2.5X), CD68+ (2.5X), and MAC387+ (1.8X) macrophages and cardiac collagen deposition (2.5X) compared to NSF and SIVnoE. They had elevated CD14+CD16+ monocytes early (8 dpi (2.8X, dpi), 19 dpi (3.1X)), and terminally (5.9X) compared to NSF and SIVnoE. Cardiac collagen correlated with CD14+CD16+ monocytes at 8 dpi (r=0.70, p<0.01) and 19 dpi (r=0.57, p<0.05) and terminally (r=0.61, p<0.05). Plasma markers were increased in CVD and SIVE animals compared to CVD and SIVE only [plasma sCD163 (2.86X); IL-18 (2.39X); galectin-3 (1.20X); and galectin-9 (1.46X)]. Plasma viral load did not differentiate. CVD and SIVE animals had increased SIV-RNA+ cells in the heart (39.5X) and CNS (3.8X) and a trend of increased SIV-gp41+ cells in the heart (9.5X) and CNS (1.7X) compared to CVD or SIVE only. No differences in the numbers of cardiac SIV-DNA+ cells were found between groups. Cardiac SIV-RNA+ cells were localized only to CD68+ and CD206+ macrophages.

**Conclusion:** Macaques with AIDS co-develop CVD and SIVE and that is correlated with increased plasma biomarkers, numbers of CD14+CD16+ monocytes, macrophage accumulation, fibrosis, and productive, but not latent SIV-infection. These findings suggest that CVD and SIVE co-morbidities in AIDS are linked and correlate with activated monocyte/macrophages.

## 404 EVIDENCE OF BRAIN HYPOXIA IN NEUROPATHOLOGY OF SARS-CoV-2–INFECTED NONHUMAN PRIMATES

**Ibolya Rutkai**[1], Meredith G. Mayer[2], Linh Hellmers[2], Bo Ning[1], Zhen Huang[1], Nicholas Maness[2], Kasi Russell-Lodrigue[2], Tony Hu[1], Chad Roy[2], Robert Blair[2], Rudolf Bohm[2], Lara A. Doyle-Meyers[2], Jay Rappaport[2], Tracy Fischer[2]
[1]*Tulane University, Metairie, LA, USA,* [2]*Tulane National Primate Research Center, Covington, LA, USA*

**Background:** Neurological manifestations are a major complication of sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and likely contribute to symptoms of "long COVID". Elucidating the mechanisms that underlie neuropathogenesis in infection is critical for identifying or developing viable therapeutic strategies. While neurological injury in infection is varied, cerebrovascular disease is seen at a high frequency among patients over 50 years of age. Additionally, microhemorrhages and hypoxic-ischemic injury are often described in brain autopsy series of human subjects who died from COVID-19. Here, we report neuropathology in aged SARS-CoV-2 infected non-human primates (NHPs) is consistent with that observed in aged human subjects and provide insight into the underlying cause.

**Methods:** Four adult Rhesus macaques and four African green monkeys were inoculated with the 2019-nCoV/USA-WA1/2020strain of SARS-CoV-2 via a multi-route mucosal or aerosol challenge. Two of each species were included as age-matched controls. Frontal, parietal, occipital, and temporal lobes, basal ganglia, cerebellum, and brainstem were interrogated through histopathological and

immunohistochemical techniques to identify and characterize the observed pathology.
**Results:** Like humans, pathology was variable but included wide-spread inflammation with nodular lesions, neuronal injury, and microhemorrhages. Neuronal degeneration and apoptosis were confirmed with FluoroJade C and cleaved caspase 3 IHC, which showed foci of positivity, particularly among cerebellar Purkinje cells. This was seen even among infected animals that did not develop severe respiratory disease but was not seen in age-matched controls. Significant upregulation of the alpha subunit of hypoxia inducible factor 1 (HIF1-α), indicative of tissue hypoxia, was observed in brain of all infected animals, regardless of disease severity. Sparse virus was detected in brain endothelial cells but did not associate with the severity of CNS injury.
**Conclusion:** SARS-CoV-2 infected NHPs are a viable animal model for advancing our current understanding of infection-associated neuropathogenesis. Upregulation of HIF1-α in brain of infected animals suggests cerebral hypoxia may underlie or contribute to neuroinflammation and neuronal injury/death and may provide some insight into neurological manifestations observed among asymptomatic patients or those only suffering mild disease.

## 405 375W MUTATION ENHANCES CD4 BINDING AND CHANGES TROPISM IN SOME CLADES

New Investigator Scholar

**Odette Verdejo-Torres**[1], Tania Allin Vargas Pavia[1], Zhongming Mou[1], Paul R Clapham[1], Maria Duenas Decamp[1]
*[1]University of Massachusetts, Worcester, MA, USA*

**Background:** It is not well known how amino acid changes within the HIV envelope (Env) regulate opening and closing of the trimer and impact on the exposure of the CD4 binding site (CD4bs). CD4bs region on the HIV-1 trimer is a major target for cross-reacting neutralizing antibodies. It is essential to understand the evolution of macrophage-tropism (mac-tropism) and develop trimer immunogens that elicit potent, broad neutralizing antibodies (bNAbs) to target Env epitopes of diverse clades and prevent or eradicate the HIV brain infection. Using a saturation mutagenesis assay called EMPIRIC, we identify 375W Env substitution, that opened the CD4bs without modifying the trimer apex (Duenas-Decamp, M et al., PLOS Pathogens, 2016). Here, we tested the effect of 375W in different Transmitted/Founder (T/F), acute stage, Mother-to-child transmission, and late state macrophage and non-macrophage primary isolates of different subtypes.
**Methods:** A tryptophan at 375 position was introduced in 25 diverse HIV-1 Envs from clades A, B, C, and D and circulating recombinant forms (CRF) (AE, and AG). To evaluate the influence of 375W mutation in CD4 binding and macrophage-tropism, we tested the sensitivity of Env+ pseudovirions to neutralization by sCD4 and infection in macrophage.
**Results:** We found that 375W mutation enhances sCD4 sensitivity in all the clades and CRF tested. This mutation increases macrophage infection in non-macrophage-tropic (non-mac-tropic) Envs. Interestingly, only three clade B macrophage-tropic (mac-tropic) primary isolates reduce macrophage infectivity when a tryptophan at position 375 was introduced. The presence of 375W mutation changes tropism in some non-mac-tropic Envs of different subtypes.
**Conclusion:** 375W mutation increases macrophage infection in almost all viruses tested and enhances the CD4 binding in all primary isolates. Moreover, this single mutation can change tropism. To protect against infection, we need to develop antigens that can elicit bNAbs that target Env epitopes of diverse subtypes. Overall, we found a mutation that expose the CD4bs in clades A, B, C, and D and CRF AE, and AG. A tryptophan at position 375 could be a good candidate to develop immunogens that induce bNAbs against mac-tropic primary isolates preventing infected individuals from developing mac-tropic variants that migrate to the brain. This vaccine may therefore target not only the formation and/or maintenance of the HIV brain reservoir, but also HIV infection.

## 406 H/L-FERRITINS AND TIM-1 ASSOCIATED WITH NEUROCOGNITIVE FUNCTION IN PEOPLE WITH HIV

**Harpreet Kaur**[1], Kunling Wu[2], Robert Kalayjian[3], Frank Palella[4], Susan L. Koletar[5], Corrilynn O. Hileman[3], William Bush[6], Kristine Erlandson[7], Ronald J. Ellis[8], Roger Bedimo[9], Babafemi O. Taiwo[4], Katherine Tassiopoulos[2], Asha R. Kallianpur[10]
*[1]Cleveland Clinic, Cleveland, OH, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]MetroHealth Medical Center, Cleveland, OH, USA, [4]Northwestern University, Chicago, IL, USA, [5]The Ohio State University, Columbus, OH, USA, [6]Case Western Reserve University, Cleveland, OH, USA, [7]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [8]University of California San Diego, San Diego, CA, USA, [9]VA North Texas Health Care Center, Dallas, TX, USA, [10]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA*

**Background:** HIV infection and inflammation alter iron homeostasis, which is essential for energy production and brain health. We previously reported that higher cerebrospinal fluid levels of the oligodendrocyte iron-delivery protein ferritin heavy-chain (Fth1) may protect against neurocognitive impairment (NCI) in people with HIV (PWH). Here, we hypothesized that higher serum Fth1 and ferritin light-chain (Ftl) levels, and lower urine levels of the Fth1 receptor, T-cell immunoglobulin and mucin domain-1 (Tim-1), are associated with less NCI in PWH.
**Methods:** In this cross-sectional analysis, we quantified serum Fth1, Ftl, inflammation markers (IL-6, TNFR2, CD163), and urine Tim-1, by ELISA (immunoassay) at entry in ACTG A5322 HIV Infection, Aging, Immune Function, and Long-term Observational (HAILO) Study enrollees. Neurocognitive function, assessed at entry by Neuroscreen, included Trailmaking A (TMA) and B (TMB), Wechsler Adult Intelligence Scale-Revised Digit Symbol (DSY) and Hopkins Verbal Learning tests (HVLT); z-scores derived from the 4 demographically adjusted component tests were averaged as the NPZ4. NCI was defined by ≥2 scores ≥1 SD below the mean, or ≥1 score ≥2 SD below the mean. Multivariable-adjusted regression models evaluated biomarker associations with component test scores, the NPZ4, and NCI, in all PWH and separately in females and males.
**Results:** Of 318 PWH with sufficient Neuroscreen data (mean age 52 years, 19% females, median CD4 nadir 215 cells/μL, 96% with HIV RNA<200 copies/mL), 82 (26%) had NCI at entry. In univariate analyses, higher Fth1 and Ftl levels were associated with reduced odds of NCI (Odds Ratio (OR) 0.72, p=0.047 and OR 0.65, p=0.015, respectively); higher Ftl was also associated with better DSY score (p=0.012). Higher urine Tim-1 was associated with lower TMB, HVLT, and NPZ4 scores (p-values 0.017, 0.019, and 0.044, respectively) and higher odds of NCI (OR 1.38, p=0.043). Multivariable-adjusted results were similar (see Table).
**Conclusion:** Higher serum Fth and Ftl levels are associated with lower odds of NCI, with stronger Ftl effects observed in females, while higher urine Tim-1 increases the odds of NCI in PWH. Tim-1 and Ftl, but not Fth1 levels, also influence performance on individual neurocognitive tests, suggesting unique mechanisms underlying the Fth1 association with NCI. Longitudinal analyses of neurocognitive outcomes are underway.

**Multivariable-Adjusted Associations**

| Marker *Units= ng/mL* | NCI (n=82 of 318) *Adj OR* (95% CI) | TMA (n=317) *Beta* (95% CI) | TMB (n=317) *Beta* (95% CI) | DSY (n=317) *Beta* (95% CI) | HVLT (n=315) *Beta* (95% CI) | NPZ4 (n=310) *Beta* (95% CI) |
|---|---|---|---|---|---|---|
| ↑Fth1 | 0.69 (0.48, 0.97)* | -0.029 (-0.216, 0.156) | 0.010 (-0.167, 0.187) | 0.072 (-0.119, 0.263) | -0.001 (-0.180, 0.177) | 0.011 (-0.125, 0.147) |
| ↑Ftl | All: 0.57 (0.40, 0.83)** | All: 0.120 (-0.052, 0.291) | All: 0.135 (-0.036, 0.306) | All: 0.273 (0.091,0.455)** | All: 0.099 (-0.075, 0.273) | All: 0.132 (0.001, 0.263)* |
| | F: 0.34 (0.14, 0.79)* M: 0.63 (0.40, 0.98)* | F: 0.588 (0.226, 0.851)** M: 0.004 (-0.185, 0.195) | F: 0.350 (0.05, 0.65)* M: 0.080 (-0.124, 0.283) | F: 0.500 (0.11, 0.89)** M: 0.207 (0.001, 0.413)* | F: 0.126 (-0.245, 0.496) M: 0.069 (-0.129, 0.266) | F: 0.360 (0.11, 0.62)** M: 0.084 (-0.070, 0.239) |
| ↑Tim-1 | 1.42 (1.03, 1.96)* | 0.001 (-0.137, 0.138) | -0.149 (-0.288,-0.010)* | -0.049 (-0.199, 0.101) | -0.146 (-0.288, -0.004)* | -0.100 (-0.206, 0.005)# |

Models were adjusted for risk factors with univariate p≤0.10: inflammation (IL-6, TNFR2, CD163) plus ≥2 of: age, sex, race/ethnicity, comorbidity, efavirenz use, nadir CD4<200, hepatitis C serology. Sex differences in effect size/statistical significance are shown. *F*=Females; *M*=Males (gender identity information is not currently available) *p<0.05; **p≤0.01; #p=0.062

## 407 CSF EXOSOME AB42 AND TAU/AB42 RATIO ASSOCIATED WITH COGNITIVE DISORDERS IN OLDER PWH

**Debjani Guha**[1], Vikas Misra[1], David Lorenz[1], Dana Gabuzda[1]
*[1]Dana–Farber Cancer Institute, Boston, MA, USA*

**Background:** HIV-associated neurocognitive disorders (HAND) remain prevalent despite viral suppression on current antiretroviral therapy (ART). Older people with HIV (PWH) are also at risk for amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD), but biomarkers to distinguish these disorders from HAND are unavailable. β-amyloid (Aβ) and Tau are associated with cognitive decline in aMCI/AD, but their relationship to HAND is unclear. Given the role of exosomes and other extracellular vesicles (EV) in neurocognitive disorders, we investigated the relationship of plasma and CSF

soluble and EV-associated Aβ42, total Tau, NFL, GFAP, ICAM-1, VCAM-1, and CRP to cognitive impairment in PWH.

**Methods:** Plasma and CSF EVs isolated from 184 participants (98 PWH virally suppressed on ART, age 30-75 years, 84% male, 52% with HAND diagnoses of asymptomatic neurocognitive impairment or mild neurocognitive disorder from NNTC/CHARTER and 86 HIV- controls matched for age, gender, race) were characterized by electron microscopy, nanoparticle tracking analysis, and immunoblotting. Soluble and EV-associated biomarkers were measured in plasma and CSF by Meso Scale Discovery platform

**Results:** The median age of PWH was 53 years (IQR 47–59) and median CD4 count, CD4 nadir, and duration of HIV infection were 540 and 84 cells/ul, and 15 years, respectively. 96% had plasma viral load <200 copies/ml. HIV infection was associated with increased plasma soluble NFL (p=0.04) and CSF soluble Aβ42 (p=0.0003), but plasma and CSF soluble Tau showed no significant difference by HIV status. In CSF EV, Aβ42 was decreased (p=0.0002) and Tau/Aβ42 ratio was increased (p=0.001) in HAND vs. no HAND. CSF EV Aβ42 correlated positively (p<0.0001) and CSF EV Tau/Aβ42 ratio (p=0.0003) and plasma soluble NFL (p=0.098) negatively with global cognitive T scores in regression models adjusted for age. Proteinase K treatment and immunoblotting confirmed enrichment of Tau and Aβ42 in CSF EV. Cerebrovascular disease was more prevalent among PWH with HAND vs. no HAND (p=0.005) and associated with increased plasma soluble NFL (p=0.03) and CSF EV Tau/Aβ42 ratio (p=0.10). Although PWH had higher levels of plasma EV ICAM-1 and VCAM-1 compared with HIV- controls (p<0.0001), HAND was not associated with these biomarkers.

**Conclusion:** Decreased CSF EV Aβ42 and increased Tau/Aβ42 ratio are associated with mild cognitive impairment in ART-treated older PWH and may help to distinguish aMCI and AD from HAND in this population.

## 408 HIGH PROTEIN CARBONYL LEVELS CORRELATE WITH ABNORMAL WHITE MATTER IN PEOPLE WITH HIV

**Patricia K. Riggs**[1], Albert M. Anderson[2], Bin Tang[1], Leah H. Rubin[3], Susan Morgello[4], Christina M. Marra[5], Benjamin B. Gelman[6], David Clifford[7], Donald Franklin[1], Robert K. Heaton[1], Ronald J. Ellis[1], Christine Fennema-Notestine[1], Scott L. Letendre[1]

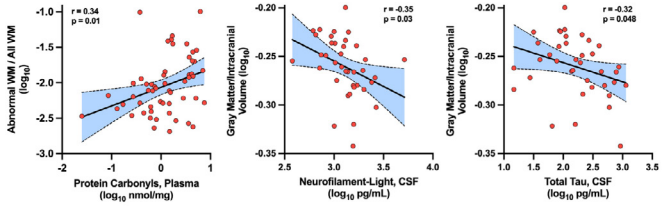
*[1]University of California San Diego, San Diego, CA, USA, [2]Emory University, Atlanta, GA, USA, [3]The Johns Hopkins University, Baltimore, MD, USA, [4]Mt Sinai School of Medicine, New York, NY, USA, [5]University of Washington, Seattle, WA, USA, [6]University of Texas Medical Branch, Galveston, TX, USA, [7]Washington University in St Louis, St Louis, MO, USA*

**Background:** Structural brain abnormalities, including those in white matter (WM), are more common in people with HIV (PWH) than in people without HIV (PWOH) but the underlying mechanisms are not known. Oxidative stress is associated with disease of many organs, including the brain. Protein carbonyls in plasma can reflect cumulative oxidative damage including in brain tissue. We asked whether plasma protein carbonyl concentration in PWH is correlated with the volume of abnormal white matter measured with magnetic resonance imaging (MRI).

**Methods:** As part of the CHARTER Aging project, a U.S. multisite, prospective, observational cohort study of PWH, we compared concentrations of soluble blood and cerebrospinal fluid (CSF) biomarkers to findings from brain structural MRI. A semi-automated multi-channel segmentation approach estimated the volume of abnormal WM normalized for total WM volume. Total gray matter (GM) volume was normalized for intracranial volume. Twelve biomarkers, including protein carbonyls (PCs) and 8-OH deoxyguanosine (8-OH-dG), were measured in blood and CSF by commercial immunoassay. Correlations and multivariable linear regression models were conducted to examine unadjusted and adjusted associations between biomarkers and imaging findings. Covariates included in the regressions included scanner, age, sex, race/ethnicity, antiretroviral therapy use, and HIV RNA in plasma, comorbidities (eg, diabetes, hypertension, HCV).

**Results:** 55 participants had both plasma biomarker and MRI data. Mean age was 56.9 years, 86.8% were men, 52.8% were either black or Hispanic, 96.2% were on ART, plasma HIV RNA <50 copies/mL in 81.6%, and median CD4+ count was 543/μL. 35 (64%) also had CSF biomarker data. Higher plasma PCs correlated with higher abnormal WM volume (p=0.011). Higher CSF neurofilament-light (NFL, p=0.029) and CSF total Tau (p=0.048) were associated with lower GM volume (Figure 1). In adjusted models, only plasma PCs remained associated with higher volume of abnormal WM (p=0.016, false discovery rate 0.026).

**Conclusion:** Protein oxidation, which has been linked to risk for Alzheimer's Disease and to conditions causing cerebral small vessel disease such as diabetes, is associated with proportionately more abnormal WM, which has been associated with cognitive impairment in PWH. If larger projects validate this finding, the results would support the hypothesis that reducing oxidative stress could treat or prevent WM injury and potentially improve cognition and daily functioning in PWH.




## 409 INTRA-INDIVIDUAL STABILITY OF CSF BIOMARKERS OVER 12 YEARS IN PEOPLE WITH HIV (PWH)

**Asante R. Kamkwalala**[1], Ankita Garg[2], Upal Roy[3], Avery Matthews[4], Patricia K. Riggs[5], Leah H. Rubin[1], Christina M. Marra[6], Susan Morgello[7], Benjamin B. Gelman[8], David Clifford[9], Donald Franklin[5], Debra Cookson[5], Robert K. Heaton[5], Ronald J. Ellis[5], Scott L. Letendre[5]

*[1]The Johns Hopkins University, Baltimore, MD, USA, [2]University of Georgia, Athens, GA, USA, [3]University of Texas Rio Grande Valley, Brownsville, TX, USA, [4]University of Texas at San Antonio, San Antonio, TX, USA, [5]University of California San Diego, San Diego, CA, USA, [6]University of Washington, Seattle, WA, USA, [7]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [8]University of Texas at Galveston, Galveston, TX, USA, [9]Washington University in St Louis, St Louis, MO, USA*

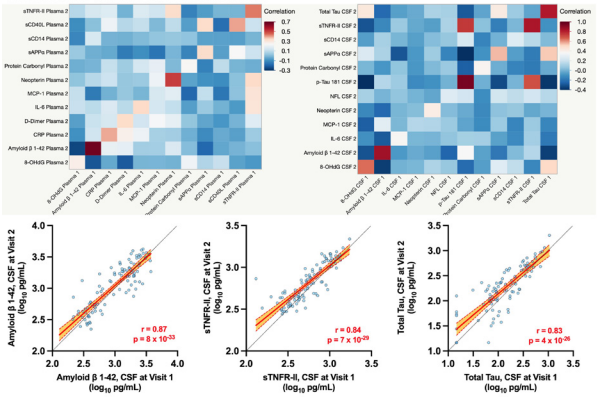
**Background:** Inflammation can persist during antiretroviral therapy (ART) and this increases the risk of neurological complications in PWH, but little is known about how biomarkers of inflammation and neurodegeneration change over many years. To address this, we assessed the intra-individual stability of biomarkers in blood (n=148 PWH) and cerebrospinal fluid (CSF, n=102 PWH) over more than decade.

**Methods:** PWH were assessed between 2003 and 2007 (Visit 1) and then again after a median 12.3 years (Visit 2) in the CHARTER Aging project. At both visits, participants took ART and completed comprehensive neuropsychiatric and medical assessments. A panel of biomarkers (see Figure) was quantified by immunoassay. Biomarker concentrations were transformed to reduce skewness. Linear regression (LR) compared biomarker concentrations between the two visits, and multivariable LR (MLR) accounted for demographic and disease characteristics.

**Results:** At Visit 2, the median age was 55 years, 17.1% were women, 43.8% were black, 84.4% had an AIDS diagnosis, 89.5% had HIV RNA in plasma ≤ 200 cp/mL, and median CD4+ T-cells were 530/μL. A correlation heatmap (Figure) summarizes comparisons of biomarkers in blood or CSF between the two visits. In blood, r values ranged from -0.25 (p=0.002) to 0.68 (p<10e-26 for amyloid β1-42). In CSF, r values ranged from -0.45 (p<10e-5) to 0.87, with particularly strong correlations (see Figure) for amyloid β1-42 (p<10e-32), soluble TNF receptors-II (p<10e-28), and total (p<10e-25) and phosphorylated Tau (p<10e-57). Correlation coefficients between the same biomarkers were stronger in CSF than in blood (median difference +0.19, p=0.018). CSF biomarker relationships did not substantially change with adjustment for age, sex, race/ethnicity, CD4+ T-cells, and HIV RNA, except for neurofilament-light, which weakened from p=0.006 to p=0.32.

**Conclusion:** Over 12 years, several biomarkers in CSF remained remarkably stable in PWH who were taking ART. Several explanations are possible. These biomarkers may be at low concentrations that do not fluctuate over time. Alternatively, they may be elevated but invariable over time, which could occur, for example, if their concentrations were genetically determined. In contrast, biomarkers in plasma varied much more over 12 years. This suggests that the biological processes underpinning neurological complications in PWH may have variable and invariable components, which could inform diagnostic and therapeutic efforts.

**Figure:** Correlation heatmap for biomarkers in blood (above left) or CSF (above right) with graphs of three examples of highly correlated CSF biomarkers (below). The diagonal line is the line of identity, the solid line is the regression line, and the shaded areas denote its 95% confidence interval.




## 410 DECREASING CNS MYELOID ACTIVATION RELATES TO DECREASING NEURODEGENERATION IN HIV

**Azin Tavasoli**[1], Scott L. Letendre[2], Benjamin B. Gelman[3], Christina M. Marra[2], David Clifford[4], Susan Morgello[5], Jennifer Iudicello[2], Leah H. Rubin[6], Ronald J. Ellis[2]

*[1]Sepidjamegan Health Center, Babolsar, Mazandaran, Iran, Islamic Republic of, [2]University of California San Diego, San Diego, CA, USA, [3]University of Texas at Galveston, Galveston, TX, USA, [4]Washington University in St Louis, St Louis, MO, USA, [5]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [6]The Johns Hopkins Hospital, Baltimore, MD, USA*

**Background:** Chronic myeloid activation and neurodegeneration are characteristic of HIV. This study sought to evaluate how changes in plasma and CSF markers of myeloid activation over 12 years related to changes in CSF markers of neurodegeneration. We hypothesized that decreasing myeloid activation would correlate with decreasing neurodegeneration in PWH.

**Methods:** PWH in the US multisite CHARTER Aging project were assessed at a baseline visit and again after 12 years using standardized evaluations. They were included in this analysis if their plasma HIV RNA was ≤50 copies/ml at follow-up and had a panel of 17 soluble biomarkers measured in plasma and CSF by immunoassay at both assessments. Participants with severely confounding medical and neuropsychiatric conditions were excluded. The difference between biomarker concentrations at the two assessments was calculated. Factor analyses were used to reduce the dimensionality of the change in biomarkers of plasma and CSF inflammation/myeloid activation and CSF neurodegeneration separately. The Bonferroni-Hochberg method accounted for type I error. Correlations between changes in inflammation/myeloid activation and neurodegeneration markers were evaluated using Pearson's r or Spearman's rho as appropriate.

**Results:** Participants were 109 ART-treated virally suppressed PWH, follow-up mean (SD) age 56.5 (8.29) years, 14.0% female, 51.4% non-white, median (IQR) current CD4+ T-cells 576 (368, 860). The plasma immune analysis yielded 2 Factors: Factor 1 loading on CRP and d-dimer, Factor 2 loading on MCP1 and sCD14. The neuro analysis yielded 2 Factors: Factor 1 loading on Amyloid β 1-42 (Aβ42) and Factor 2 loading on neurofilament-light (NFL). The CSF immune factor analysis yielded 2 Factors with Factor 1 loading on sTNFR2 and neopterin and Factor 2 loading on MCP-1 and sCD14. CSF immune Factor 2 correlated with plasma immune Factor 1 (p=0.0126). Decreases in CSF immune Factor 2 (MCP-1/sCD14) correlated with decreases in CSF neuro Factor 2 (CSF NFL) (r=0.370, p=0.0002, Bonferroni p=0.0007). Age, sex and ethnicity did not significantly influence any of the other plasma or CSF immune or CSF neuro Factors.

**Conclusion:** These findings support the hypothesis that reduction of myeloid activation, as reflected in CSF MCP-1 and sCD14, but not systemic inflammation is linked to reductions in neurodegeneration in virally suppressed PWH. Results raise the possibility that successful reduction of myeloid activation could reduce neurodegeneration in virally suppressed PWH.

**Biomarkers in the analysis and Factor analyses**

| Immune | Neuro | Immune F1 | Immune F2 | Neuro F1 | Neuro F2 |
|---|---|---|---|---|---|
| sCD40L – plasma only | NFL – CSF only | sTNFR2 | MCP-1 | Ab42 | NFL |
| IL-6 – plasma, CSF | total Tau – CSF only | neopterin | sCD14 | | |
| sTNFR2 – plasma, CSF | Phosphoryl-ated tau - CSF only | | | | |
| CRP – plasma only | Ab42 – CSF, plasma | | | | |
| Neopterin – plasma, CSF | sAPP – CSF, plasma | | | | |
| MCP-1 – plasma, CSF | | | | | |

## 411 SERUM AND CSF ULTRA-SENSITIVE DETECTION OF NFL AND ALZHEIMER'S BIOMARKERS IN PLWH

**Mattia Trunfio**[1], Miriam Antonucci[2], Jessica Cusato[1], Daniela Vai[1], Daniele Imperiale[1], Antonio D'Avolio[1], Stefano Bonora[1], Giovanni Di Perri[1], Andrea Calcagno[1]

*[1]University of Turin, Turin, Italy, [2]Amedeo di Savoia Hospital, Torino, Italy*

**Background:** Aging PLWH have increased risk of HIV-associated neurocognitive disorders and may experience early neurodegeneration mimicking Alzheimer's disease (AD). Studies on biomarkers for such complications report discordant findings also due to laboratory assays sensitivity especially in effectively controlled infections. We measured serum/CSF neurofilament light chain (NFL) and AD biomarkers with a new digital based on Single Molecule Array (Simoa SR-X, Quanterix®) and assessed neurocognitive correlates in PLWH on effective cART

**Methods:** Cross-sectional observational pilot study. Adult PLWH on cART with plasma and CSF HIV-RNA<50 cp/mL, without major neuropsychological confounding, undergoing lumbar puncture and neurocognitive assessment (15 tests) for research purposes were enrolled. Total tau (tau), 181-phosphorylated tau (ptau), amyloid β fragments 42 (β42) and 40 (β40) were quantified by Neuro 3-Plex Advantage assay® (mean limit of detection LOD 0.10 pg/mL) and NFL by NF-light A assay® (LOD 0.038 pg/mL) in coupled serum/CSF samples. Data are expressed as median (interquartile range)

**Results:** 44 patients enrolled. 95.4% Caucasian, 75% male; median age and current CD4+ count were 54 years (50-61) and 439 cells/mmc (329-719). Serum/CSF levels (pg/mL) were: NFL 9.6 (6.8-21.7)/716.1 (390.9-1227.7); tau 1.3 (0.9-1.8)/123.0 (20.0-221.6); ptau 6.4 (4.5-9.1)/288.4 (168.9-688.9); β40 184.7 (145.1-215.7)/6878.8 (3671.0-14573.4); β42 9.3 (5.3-11.7)/462.8 (289.3-1089.5). Strong correlations between serum and CSF NFL and tau levels were observed, while such a correspondence was not observed for the others (Fig.1). Surprisingly, serum and not CSF biomarkers correlated with scores in several cognitive domains: as ex. NFL with Corsi (ϱ-42, p.009), verbal fluency (VF; ϱ-76, p.03) and copy of Osterrieth figure (ϱ-42, p.01); β42 with VF (ϱ-84, p.03); tau with VF (ϱ-85, p.02), and immediate and delayed free and cued selective reminding (ϱ-38, p.04 and ϱ-49, p.007). CSF biomarkers correlated with other markers of local inflammation: NFL with CSF-serum albumin ratio (ϱ 36, p.02) and CSF proteins (ϱ 49, p.004); β40-β42 with CSF cells (ϱ 41, p.02-ϱ 42, p.02); tau with CSF cells (ϱ 39, p.02), proteins (ϱ 35, p.04) and Tibbling index (ϱ-48, p.001)

**Conclusion:** These data are the first evaluating SIMOA-based ultra-sensitive detection in this field; further studies are warranted to validate these results and to assess whether and why serum and not CSF NFL and AD biomarkers better correlated with neurocognition in PLWH.

**Fig.1 Spearman rank-order correlation coefficients of serum and CSF NFL and Alzheimer's disease biomarkers in the study sample (n=44) (ϱ upper value; p-value lower value)**

| | Serum NFL | CSF NFL | Serum β40 | CSF β40 | Serum β42 | CSF β42 | Serum Tau | CSF Tau | Serum pTau | CSF pTau |
|---|---|---|---|---|---|---|---|---|---|---|
| Serum NFL | | .762<br>.0005 | .316<br>.133 | .017<br>.922 | .018<br>.933 | -.040<br>.810 | .540<br>.002 | .338<br>.027 | -.064<br>.808 | .235<br>.363 |
| CSF NFL | .762<br>.0005 | | .256<br>.228 | .285<br>.082 | -.013<br>.951 | .139<br>.406 | .624<br>.0005 | .578<br>.0005 | -.238<br>.341 | .098<br>.699 |
| Serum β40 | .316<br>.133 | .256<br>.228 | | .260<br>.220 | .763<br>.0005 | .202<br>.344 | .245<br>.248 | .433<br>.035 | .830<br>.003 | .382<br>.276 |
| CSF β40 | .017<br>.922 | .285<br>.082 | .260<br>.220 | | .320<br>.119 | .914<br>.0005 | .201<br>.336 | .783<br>.0005 | .685<br>.014 | .601<br>.039 |
| Serum β42 | .018<br>.933 | -.013<br>.951 | .763<br>.0005 | .320<br>.119 | | .345<br>.092 | -.115<br>.583 | .230<br>.269 | .773<br>.005 | .345<br>.298 |
| CSF β42 | -.040<br>.810 | .139<br>.406 | .202<br>.344 | .914<br>.0005 | .345<br>.092 | | .093<br>.658 | .583<br>.0005 | .706<br>.010 | .657<br>.020 |
| Serum Tau | .540<br>.002 | .624<br>.0005 | .245<br>.248 | .201<br>.336 | -.115<br>.583 | .093<br>.658 | | .729<br>.0005 | -.029<br>.914 | -.047<br>.863 |
| CSF Tau | .338<br>.027 | .578<br>.0005 | .433<br>.035 | .783<br>.0005 | .230<br>.269 | .583<br>.0005 | .729<br>.0005 | | .063<br>.804 | .174<br>.489 |
| Serum pTau | -.064<br>.808 | -.238<br>.341 | .830<br>.003 | .685<br>.014 | .773<br>.005 | .706<br>.010 | -.029<br>.914 | .063<br>.804 | | .443<br>.066 |
| CSF pTau | .235<br>.363 | .098<br>.699 | .382<br>.276 | .601<br>.039 | .345<br>.298 | .657<br>.020 | -.047<br>.863 | .174<br>.489 | .443<br>.066 | |

Non-significant correlation | Mild-moderate correlation | Strong correlation

## 412 ASSOCIATIONS BETWEEN PLASMA BIOMARKERS AND NEUROCOGNITION IN ART-TREATED PWH

**Robert Kalayjian**[1], Corrilynn O. Hileman[1], Ronald J. Ellis[2], Asha R. Kallianpur[3], Roger Bedimo[4], Kristine Erlandson[5], Susan L. Koletar[6], Babafemi O. Taiwo[7], Kunling Wu[8], Frank Palella[7], Katherine Tassiopoulos[8]
*[1]Case Western Reserve University, Cleveland, OH, USA, [2]University of California San Diego, San Diego, CA, USA, [3]Cleveland Clinic Foundation, Cleveland, OH, USA, [4]University of Texas Southwestern, Dallas, TX, USA, [5]University of Colorado, Denver, CO, USA, [6]Ohio State University, Columbus, OH, USA, [7]Northwestern University, Chicago, IL, USA, [8]Harvard TH Chan School of Public Health, Boston, MA, USA*

**Background:** Inflammation, due in part to impaired gut integrity, may contribute to neurocognitive impairment (NCI) in people with HIV (PWH). We examined associations between plasma biomarkers of inflammation and gut integrity with prevalent and incident NCI, and with cognitive trajectories in participants of a multicenter, prospective cohort study (HIV Infection, Aging, and Immune Function Long-Term Observational study; HAILO, ACTG Study A5322) of older PWH (age >40 at entry) receiving ART.

**Methods:** Biomarker levels were quantified by ELISA at HAILO entry and normalized as Z-scores (by subtracting from the mean and dividing by the S.D.). Neurocognition was assessed at HAILO entry, and every 48 weeks by: Trailmaking A & B, Wechsler Adult Intelligence Scale-Revised Digit Symbol, and Hopkins Verbal Learning tests. Demographically adjusted scores were converted to Z-scores and averaged (as NPZ4). NCI was defined by ≥2 domains ≥1 S.D. below the norm, or ≥1 domain ≥2 S.D. below the norm. Multivariable logistic regression examined associations by biomarker levels with prevalent NCI at entry; Cox Proportional Hazard and mixed effects linear models examined associations with incident NCI, and with NPZ4 slopes, respectively, among participants without NCI at entry.

**Results:** 363 PWH were included, randomly selected among 971 HAILO participants. Median age 51 yrs; 19% were female at birth (gender not collected), 27% Black, and 24% Hispanic; median entry CD4 was 617cells/μL; 96% maintained viral suppression to <200 copies HIV-RNA /mL throughout a median follow-up of 192 wks. The average NPZ4 slope did not differ from zero (P=0.75). Higher sTNFR-1&-2, & sCD163 levels associated with increased odds of prevalent NCI and there was some evidence of an association with lower IFAB. Higher sTNFR-1 associated with increased hazard of incident NCI and there was some evidence of an association with higher sCD163. Higher sTNFR-2 also associated with a faster rate of cognitive decline and there was some evidence of an association with higher sTNFR-1.

**Conclusion:** These findings support the importance of inflammation in the pathogenesis of NCI in ART-treated PWH.

| Biomarker | Prevalent NCI at entry; n=93 | Incident NCI; n=90 of 261 | NPZ4 Slope; n=261 |
|---|---|---|---|
| | Adj OR (95% C.I.) per each 1 S.D. Biomarker Increment | Adj HR (95% CI) per each 1 S.D. Biomarker Increment | ΔNPZ4 (95% CI)/yr per each 1 S.D. Biomarker Increment |
| sTNFR2 | 1.41 [1.10, 1.81]* | 1.28 [1.04, 1.58]* | −0.031 [−0.054, −0.008]** |
| sCD163 | 1.40 [1.02, 1.91]* | 1.26 [0.97, 1.64]§ | −0.005 [−0.032, 0.021] |
| sTNFR1 | 1.31 [1.05, 1.64]* | 1.14 [0.96, 1.35] | −0.019 [−0.042, 0.002]§ |
| IL-6 | 1.02 [0.81, 1.28] | 1.07 [0.95, 1.20] | 0.002 [−0.008, 0.012] |
| sCD14 | 1.01 [0.78, 1.30] | 1.05 [0.85, 1.28] | 0.005 [−0.025, 0.015] |
| VEGF | 0.90 [0.70, 1.18] | 1.10 [0.91, 1.35] | 0.027 [−0.006, 0.060] |
| IFAB | 0.73 [0.05, 1.03]§ | 0.99 [0.81, 1.22] | 0.003 [−0.014, 0.021] |

Adjusted for: age, sex, race/ethnicity, ART duration, education status, nadir CD4 and time-updated CD4 & HIV-RNA.
sTNFR=soluble tumor necrosis factor; IL=interleukin; VEGF= vascular endothelial growth factor;
IFAB=intestinal fatty acid binding protein; §P<0.10, *P<0.05, **P<0.01

## 413 SERUM NEUROFILAMENT AS A MARKER OF WHITE MATTER INJURITY IN HIV DISEASE

**Christina S. Meade**[1], Sheri L.Towe[1], David M. Murdoch[1], Ryan P. Bell[1]
*[1]Duke University, Durham, NC, USA*

**Background:** White matter degradation in HIV disease partly reflects legacy effects of untreated infection. Despite effective therapy, persistent immune activation may contribute to further neurodegeneration. Neurofilament light (NFL) is a biomarker of axonal injury that can be measured in biofluids, but direct correlation with MRI measures of white matter integrity in HIV has not been investigated.

**Methods:** We recruited adults with chronic HIV disease who were on antiretroviral therapy with sustained virologic suppression for >1 year. Participants completed diffusion-weighted and high-resolution anatomical imaging on a 3T MRI scanner, followed by a blood draw. Serum samples were analyzed using an ultrasensitive enzyme-linked immunosorbent assay on a single molecule array platform. Whole-brain voxel-wise analyses related NFL to MRI metrics, adjusting for age. MRI metrics consisted of fractional anisotropy (FA), mean diffusivity (MD), and gray and white matter volume.

**Results:** The sample included 108 participants [81% male, 76% African American, M= 45.4 (9.7) years]. Participants had been living with HIV for a median of 13.0 years (IQR= 9.0, 21.0), with a median nadir CD4 of 195.5 (IQR= 53.8, 324.0), and 72% had current CD4 counts >500 copies. In a tract-based spatial statistics analysis, NFL correlated negatively with FA broadly across most tracts (Figure 1), but there was no relationship between NFL and MD. Voxel-based morphometry confirmed no correlation with white or gray matter volume. Participants with current CD4 T-cell counts <350 had higher NFL compared to others [8.57 (.69) vs. 6.73 (.27); F(2,108)= 6.05, p= .016], suggesting that immunosuppression may contribute to ongoing axonal injury.

**Conclusion:** NFL is a useful marker of the microstructural integrity of white matter in PWH. However, it may not capture other neurodegenerative processes, such as cellularity and necrosis, and effects cannot be localized to specific tracts. Neuroimaging, used in combination with laboratory tests, remains an invaluable tool for visualizing structural changes in neurodegenerative disease. Longitudinal studies are needed to investigate the utility of NFL for predicting change in white matter integrity over time.

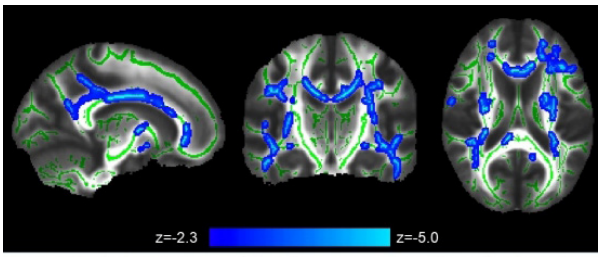



**Figure 1**. Voxel-wise negative correlation of serum neurofilament to fractional anisotropy using tract based spatial statistics, controlling for age (p<.05, Threshold-Free Cluster Enhancement corrected for multiple comparisons).

## 414 PLASMA D-DIMER, A MARKER OF INFLAMMATION, IS INCREASED WITH POLYNEUROPATHY IN HIV

**Ronald J. Ellis**[1], David Clifford[2], Christina M. Marra[3], Ann C. Collier[3], Benjamin B. Gelman[4], Jessica Robinson-Papp[5], Scott L. Letendre[1], J. Allen McCutchan[1], Robert K. Heaton[6]
*[1]University of California San Diego, San Diego, CA, USA, [2]Washington University in St Louis, St Louis, MO, USA, [3]University of Washington, Seattle, WA, USA, [4]University of Texas at Galveston, Galveston, TX, USA, [5]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [6]University of California San Diego, La Jolla, CA, USA*

**Background:** Plasma D-dimer is a marker of coagulation and inflammation, both of which may be associated with sensory polyneuropathy in a variety of disorders such as diabetes mellitus, but this has not been examined in HIV-associated distal sensory polyneuropathy (DSP). We therefore assessed the cross-sectional correlation between plasma D-dimer levels and HIV DSP.

**Methods:** Participants in the prospective, observational CNS HIV AntiRetroviral Therapy Effects Research (CHARTER) cohort underwent standardized clinical evaluations for clinical examination findings of distal sensory polyneuropathy (DSP) and reported distal neuropathic pain. D-dimer was measured by immunoassay, and values were $\log_{10}$ transformed to improve their distribution for parametric analysis. Relationships between D-dimer and DSP were evaluated using Pearson correlation and multivariable regressions including age and other relevant covariates.

**Results:** Results: Participants were 183 PWH evaluated between 2016-2020, mean (SD) age 56.2 (8.10), 19.7% women, 56.4% non-white, median nadir and current CD4 lymphocytes 107 (IQR 20, 210) and 567 (348, 817), undetectable plasma HIV RNA 79.9%. $\text{Log}_{10}$ plasma D-dimer levels showed a dose response relationship to the number of neuropathy signs: $2.76 \pm 0.225$ for those with 0 signs ($N = 50$), $2.70 \pm 0.206$ for those with 1 sign ($N = 47$) and $2.83 \pm 0.241$ for those with >= 2 signs ($N = 88$) ($p = 0.0068$). Effect sizes were 0.544, 0.324 and 0.220, respectively. Older age was also associated with the number of neuropathy signs ($p < 0.0001$). In a multivariable regression, both age ($p =$ 9.75e-8) and D-dimer ($p = 0.0045$) were independently associated with DSP (≥ 2 signs). This relationship was in the same direction, but not significant for the subsets with detectable and undetectable HIV RNA (ps 0.139 and 0.272). Neuropathy signs were not related to diabetes or to current or nadir CD4 or plasma HIV RNA (ps > 0.20). Neuropathy symptoms, including neuropathic pain, were not related to D-dimer levels.

**Conclusion:** Chronic coagulation abnormalities and inflammation in PWH despite viral suppression may contribute to neuropathy, raising the possibility that anti-inflammatory treatments or treatments to normalize coagulation may reduce susceptibility to neuropathy.

## 415 MtDNA HAPLOGROUPS AND COGNITIVE FUNCTION IN BLACK AND HISPANIC WOMEN WITH HIV

**Todd Hulgan**[1], Tebeb Gebretsadik[2], Karen E. Volpe[2], Leah H. Rubin[3], Pauline Maki[4], Gayle Springer[3], Asha R. Kallianpur[5], Bradley Aouizerat[6], David Samuels[2]
*[1]Vanderbilt University Medical Center, Nashville, TN, USA, [2]Vanderbilt University, Nashville, TN, USA, [3]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [4]University of Illinois at Chicago, Chicago, IL, USA, [5]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA, [6]New York University, New York, NY, USA*

**Background:** Mitochondrial DNA (mtDNA) variation is related to cognitive impairment in non-White persons with HIV, based on analyses in predominantly male cohorts. As these findings may not be generalizable to women with HIV (WWH), we examined mtDNA haplogroup-cognition associations in WWH of color.

**Methods:** WWH of self-reported Black race and/or Hispanic ethnicity, enrolled in the Women's Interagency HIV Study with neuropsychological (NP) data collected from 2009-13, were included in cross-sectional analyses. mtDNA haplogroups were determined by array-based genotyping and HaploGrep. NP assessments were used to derive demographically-adjusted continuous T-scores and clinical rating scores (1-9; higher=poorer performance) in 7 cognitive domains. Cognitive impairment was defined by a rating score ≥4. Haplogroups previously associated with cognitive function (L2a in Black and B in Hispanic persons) were pre-specified for comparisons. Ordinary least squares and logistic regression models were used to examine associations, adjusting for CD4 T-cell nadir, current plasma HIV RNA and antiretroviral therapy use, body mass index, and hepatitis C virus status.

**Results:** Analyses included 571 Black and 120 Hispanic WWH with NP data. Haplogroup frequencies (L2a=20%; B=10%) were as expected for ancestry. Among Black WWH, haplogroup L2a was not significantly associated with domain T-scores, but motor and processing speed impairments were less likely in haplogroup L2a than in other haplogroups (15 vs. 23%, adjusted odds ratio [aOR] 0.55 [95% CI 0.31-0.99], p=0.05 and 19 vs. 30%, aOR 0.57 [95% CI 0.34-0.96], p=0.03). Among Hispanic WWH, T-scores for all domains except verbal memory were higher in haplogroup B than other haplogroups (β=2.2-7.1), with significantly higher motor T-score (β=7.1, 95% CI 0.4-13.7; p=0.04). Impairment in haplogroup B ranged from 0-17% vs. 13-28% in other haplogroups across 6 of 7 domains (excluding verbal memory, with 25% of both groups impaired); small sample size precluded logistic regression analyses of impairment.

**Conclusion:** Prior associations of mtDNA haplogroup B with better cognitive function were replicated in these Hispanic WWH. Motor function was significantly better, perhaps suggesting a role for mtDNA variation in neuromuscular function. Impairment in 2 domains (including motor) was less likely in Black WWH with haplogroup L2a, differing from prior results, perhaps due to cohort or sex-related differences. Future studies will assess longitudinal cognitive outcomes.

## 416 EFFECTS OF AIR POLLUTANTS ON NEUROIMAGING MEASURES DIVERGE

**Julie K. Wisch**[1], Ruth Alemu[1], Sarah Cooley[1], Anna H. Boerwinkle[1], Alexander Rosenow[1], Beau M. Ances[1]
*[1]Washington University in St Louis, St Louis, MO, USA*

**Background:** The Lancet Commission on Public Health attributes about 1 in 6 deaths to pollution related factors. The U.S. National Assessment of the Potential Consequences of Climate Variability and Change predicts that individuals living with HIV (PLWH) will be exceptionally vulnerable to climate-sensitive health outcomes. Most literature on HIV and pollution examines international cohorts, emphasizing childhood development, risks of infection and cardiovascular effects. We look at a community-dwelling cohort of older PLWH in the greater St. Louis area. We evaluate the effects of common air pollutants, including fine particulate matter (PM2.5) and ozone on cognitive performance and brain structure.

**Methods:** We collected cognitive and neuroimaging measures for 290 community dwelling individuals (208 PLWH, 82 HIV uninfected controls, 69% male). The EPA measures airborne pollutants at multiple monitoring sites throughout the region. We used home addresses and spatial interpolation to estimate the average exposure to pollutants in the week prior to a study visit. We performed multiple linear regressions with each cognitive and neuroimaging measure as the response variable and an interaction between the measured pollutant and HIV status as the regressor. We controlled for age, sex, education, and neighborhood-level socioeconomic status. We applied Bonferroni correction for multiple cognitive/neuroimaging measures.

**Results:** A 10 µg/mL increase in average exposure to PM2.5 in the week prior to assessment was associated with a decrease in performance on the learning domain assessments by about 1 standard deviation (pcorrected = 0.034). We also observed a significant interaction between HIV status and ozone exposure. When HIV-seronegative individuals are exposed to high levels of ozone, they had increases in cerebral blood flow in the superior parietal lobe; however, PLWH did not show the same response (pcorrected = 0.027). HIV-seronegative individuals have a negative relationship between temporal lobe volume and ozone exposure, while PLWH have a positive relationship between temporal lobe volume (pcorrected = 0.030).

**Conclusion:** We find cognitive changes consistent with previous literature that points to the deleterious impacts of PM2.5 on cognition. We also find differential effects of HIV on cerebral response to ozone. This is important because of the elevated vulnerability of PLWH, and future work should focus on understanding the implications of this divergent response.

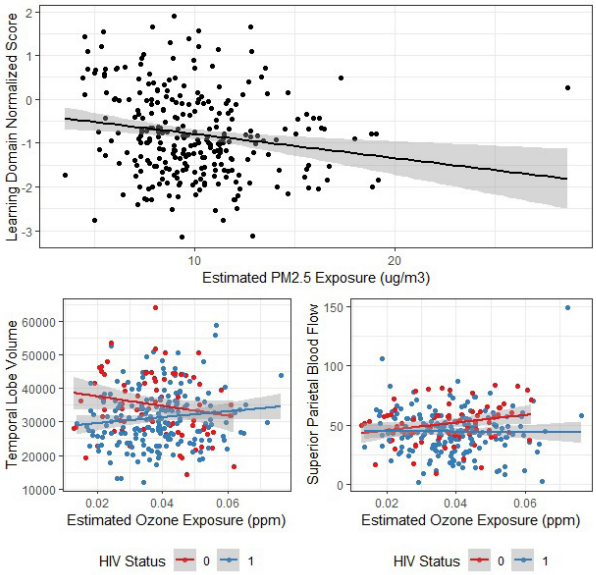



Figure 1. Regardless of HIV status, individuals perform worse on Learning Domain cognitive assessments with higher exposure to fine particulate matter (PM2.5). Temporal lobe volume associations with ozone exposure diverge depending on HIV status. Individuals living with HIV do not increase blood flow to the superior parietal region in response to elevated ozone exposure; however, HIV-seronegative individuals do.

## 417 DECREASED MYELIN CONTENT AND COGNITIVE PERFORMANCE IN ADULTS WITH PERINATAL HIV

**Payal B. Patel**[1], Alyssa Vecchio[2], Lydia Barakat[3], Thor Wagner[4], Ann J. Melvin[4], Jennifer Chiarella[3], Shannon Kolind[5], Michael Hoff[1], Adam Dvorak[5], Irene Vavasour[5], Serena S. Spudich[3], Christina M. Marra[1], Robert Paul[6], Swati Rane[1]
*[1]University of Washington, Seattle, WA, USA, [2]University of New Mexico, Albuquerque, NM, USA, [3]Yale University, New Haven, CT, USA, [4]Seattle Children's Hospital, Seattle, WA, USA, [5]University of British Columbia, Vancouver, Canada, [6]University of Missouri St Louis, St Louis, MO, USA*

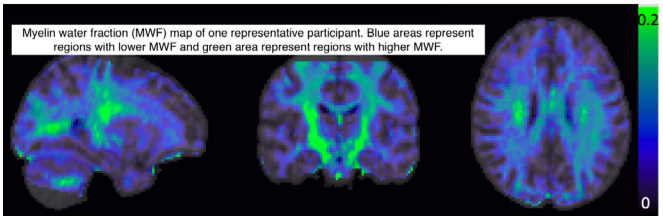
**Background:** Little is known about the cognitive profile of adults with virally suppressed perinatally acquired HIV (pHIV). Additionally, conventional and diffusion tensor imaging has not identified a robust signature of cerebral white matter injury in HIV and the microstructural pathology occurring in the white matter tracts of individuals with pHIV remains unknown. Myelin water imaging (MWI), a novel imaging modality, quantifies myelin content using differences in relaxation times of water contained in the myelin bilayer and free water. We define the cognitive profile of virally suppressed adults with pHIV and demonstrate the association between myelin water fraction (MWF), a metric of myelin content obtained through MWI, and cognition in our cohort.

**Methods:** Seventeen adults with pHIV (ages 21-36 years, 11 Female and 6 Male), virally suppressed on antiretroviral therapy (ART), underwent an 11-test

cognitive battery covering seven domains. Raw scores were adjusted for age, education, sex, and race/ethnicity. Domain specific z-scores were determined using normative data. Cognitive impairment was defined as >1.5 standard deviations below the normative mean in 2 or more domains. Eight participants underwent MWI. A Gradient and Spin Echo acquisition sequence was used for MWI data processing. Global and frontal lobe MWF was compared to 16 historical age and sex matched controls. Correlations were assessed using Spearman rank correlation coefficient.

**Results:** Ten (58%) adults living with pHIV were cognitively impaired with the lowest scores in the gross motor (average z-score: -2.9) and verbal memory (average z-score: -1.5) domains. Global and frontal lobe MWF was lower in the pHIV cohort compared to matched uninfected controls (mean global and frontal MWF: pHIV: 0.071, 0.051; controls: 0.095, 0.081; p<0.0001). Lower global MWF correlated with worse performance in the executive function domain in adults with pHIV (Spearman r: 0.762, p: 0.037).

**Conclusion:** Cognitive impairment is common among our cohort of adults with virally suppressed pHIV, particularly in the gross motor domain. This may be due to a legacy effect on motor development as individuals in this cohort were born during a period when access to ART was limited. Our pilot imaging data suggest that decreased axonal myelination may occur in individuals with well controlled pHIV. Given the strong correlation between MWF and executive function scores, this reduction in myelination may be a pathologic substrate of pHIV-related cognitive impairment.




## 418 CHILDHOOD TRAUMA MODIFIES BRAIN MORPHOLOGY AND COGNITION IN PEOPLE WITH HIV

**Lillian Ham**[1], Hsing-Chuan Hsieh[2], Erin Kelly[1], Xiuping Chu[2], Anuradha Ganesan[2], Gregory Utz[2], Ryan C. Maves[3], Ilyssa Silverman[1], Edmund Tramont[1], Stanley I. Rapoport[1], Avindra Nath[1], Brian Agan[2], Joseph Snow[1], Bryan R. Smith[1], Suad Kapetanovic[4]

*[1]National Institutes of Health, Bethesda, MD, USA, [2]Henry M Jackson Foundation, Bethesda, MD, USA, [3]Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [4]University of Southern California, Los Angeles, CA, USA*

**Background:** Growing evidence suggests a combined, detrimental effect of childhood trauma (ChT) and HIV on brain morphology and neurocognition; however, this evidence is limited by female-only cohorts with uncontrolled viremia or limited antiretroviral therapy (ART) use. We explored how ChT modifies the relation between brain morphology, and cognition and daily functioning in a diverse, US cohort of virally-suppressed people living with HIV (PLWH).

**Methods:** All PLWH (N=245) received ART and had a viral load <200 c/mL for ≥1 year. PLWH were ChT+ if they experienced physical or sexual abuse, or witnessed domestic violence in childhood. PLWH completed a 7-domain neurocognitive battery and 3 measures of daily functioning. Neurocognitive impairment (NCI) was determined using the global deficit score method. Volume (cm3; gray matter [GM], white matter, basal ganglia [BG]) and average cortical thickness (mm) were extracted using FreeSurfer. Cross-sectional analyses used multiple regressions adjusting for cohort, demographics, and years of untreated HIV.

**Results:** See table (66.9% ChT+ PLWH). There were significant interactions (ChT x brain morphology) for NCI, learning, memory, verbal fluency, and daily functioning. Simple effects analyses by ChT showed that for ChT- PLWH only, greater total GM (OR=.98, p=.012) and cortical thickness (OR=.02, p=.012) decreased odds of NCI. For ChT- PLWH, greater total GM was related to better learning (B=.05, p=.010) and memory (B=.05, p=.003); greater putamen was marginally related to better memory (B=2.02, p=.062) and verbal fluency (B=1.91, p=.069). For ChT+ PLWH, greater caudate was related to worse learning (B=-2.14, p=.012), greater pallidum to worse memory (B=-3.11, p=.048), and greater total GM to worse verbal fluency (B=-0.02, p=.026). Greater cortical thickness was related to fewer functional declines in ChT- PLWH (B=-2.29, p=.031), but this interaction was not significant in the adjusted model.

**Conclusion:** Better learning, memory, verbal fluency, and daily functioning were related to greater brain volumes and cortical thickness for ChT- PLWH, but not for ChT+ PLWH. For ChT+ PLWH, there was an inverse relationship between BG volume, and memory and learning, with no effect on psychomotor speed; however, more detailed studies are needed to assess motor function. This relationship is counterintuitive and possibly related to inflammation. Though well-controlled HIV mitigates these deficits, ChT may stunt benefits of increased GM volume and cortical thickness in PLWH.

| | Childhood Trauma | | | |
|---|---|---|---|---|
| | No (n = 81) | Yes (n = 164) | Total (N = 245) | *p*-value |
| Cohort | | | | **0.011** |
| NIH[a] | 30(37.0) | 89(54.3) | 119(48.6) | |
| DoD[b] | 51(63.0) | 75(45.7) | 126(51.4) | |
| Male sex | 75(92.6) | 117(71.3) | 192(78.4) | **<0.001** |
| Enrollment age (yrs) | 47.5(10.8) | 49.3(9.6) | 48.7(10.0) | 0.127 |
| Race | | | | **0.019[c]** |
| Caucasian/White | 46(56.8) | 67(40.9) | 113(46.1) | |
| African American/Black | 27(33.3) | 82(50.0) | 109(44.5) | |
| Other | 8(9.9) | 14(8.6)[d] | 22(9.0) | |
| Education degree | | | | 0.196 |
| Less than 12th grade | 4(4.9) | 24(14.6) | 28(11.4) | |
| 12th grade/GED | 15(18.5) | 32(19.5) | 47(19.2) | |
| Some college | 26(32.1) | 50(30.5) | 76(31.0) | |
| Bachelor's degree | 19(23.5) | 29(17.7) | 48(19.6) | |
| Higher degree | 17(21.0) | 27(16.5) | 44(18.0) | |
| Neurocognitive impairment (NCI) | 14(17.3) | 41(25.0) | 55(22.4) | 0.173 |
| Years of untreated HIV | 2.8(5.4) | 4.8(7.1) | 4.1(6.6) | **0.044** |

*Notes.* Numbers in parentheses indicate percentage. [a]National Institutes of Health (recruited community-dwelling participants in the DC metropolitan area). [b]Department of Defense (recruited military beneficiaries in the DC metropolitan area and San Diego, CA). [c]White versus non-White comparison. [d]Race was missing in 1 one participant with history of childhood trauma.

## 419 BRAIN VOLUMETRICS DIFFER BY FIEBIG STAGE IN ACUTE INFECTION

**Jacob Bolzenius**[1], Napapon Sailasuta[2], Andrew Belden[1], Phillip Chan[3], Carlo Sacdalan[3], Julie Ake[4], Somchai Sreepleanjan[3], Khunthalee Benjapornpong[3], Denise C. Hsu[4], Sandhya Vasan[4], Torie Tsuei[5], Serena S. Spudich[6], Victor Valcour[5], Robert Paul[1]

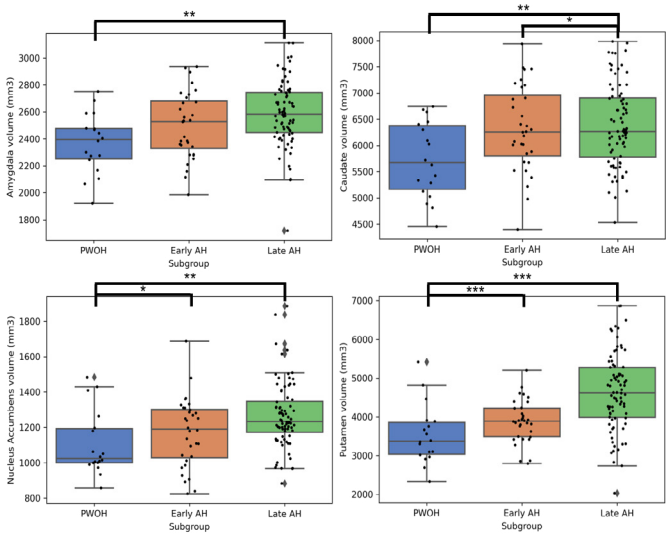
*[1]University of Missouri St Louis, St Louis, MO, USA, [2]University of Hawaii, Honolulu, HI, USA, [3]SEARCH, Bangkok, Thailand, [4]US Military HIV Research Program, Silver Spring, MD, USA, [5]University of California San Francisco, San Francisco, CA, USA, [6]Yale University, New Haven, CT, USA*

**Background:** People with chronic HIV exhibit neuroimaging abnormalities compared to people without HIV (PWOH), including lower regional brain volumes. Whether volumetric differences exist during acute HIV (AH) is unknown. The present study examined brain volume by Fiebig stage in a large sample of people with AH (PWAH) enrolled in RV254/SEARCH 010, compared to demographically similar PWOH enrolled in RV304/SEARCH 013.

**Methods:** Participants included 112 Thai males with AH (age 20-46) and 18 male and age-matched (age 18-40) Thai PWOH with no existing co-infections. PWAH were stratified into early (Fiebig I-II; n=32) vs. late (Fiebig III-V; n=80) AH based on Fiebig staging performed after enrollment. T1-weighted scans were acquired using a 3T Philips Ingenia MRI performed within 5 days of ART initiation (on or before day of ART initiation in 64%). Volumes for the caudate, putamen, pallidum, thalamus, amygdala, hippocampus, and nucleus accumbens were summed between hemispheres, corrected for differences in head size, and compared across groups using ANOVAs with false discovery rate for multiple comparisons.

**Results:** Early AH individuals had equivalent median CD4 T cell count (326 vs. 319 cells/$mm_3$), but significantly lower median CD8 T cell count (366 vs. 648 cells/$mm_3$) and lower average plasma viral load (5.31 vs. 6.42 $log_{10}$ copies/mL) than late AH individuals (both ps < .01). Late AH individuals exhibited significantly larger volumes in the caudate (11% larger), putamen (31%), pallidum (19%), amygdala (9%), and nucleus accumbens (15%) compared to PWOH (corrected ps < .05; Figure). Late AH individuals also had significantly larger putamen (19% larger) and nucleus accumbens (8%) volumes compared to early AH individuals (corrected ps < .05).

**Conclusion:** These findings suggest that brain volume in AH varies as a function of duration of infection, indicated by Fiebig stage. Larger volumes in later Fiebig stages may reflect neuroinflammatory processes during acute infection. Longitudinal research is needed to determine whether differences in brain volume persist or resolve after sustained use of ART. Additional examination of immune markers in combination with brain metabolites using spectroscopy will be critical to characterize relationships between brain structure and immune responses after acute infection.




## 420 INCREASED PHYSICAL STRENGTH IS ASSOCIATED WITH IMPROVED BRAIN INTEGRITY IN OLDER PLWH

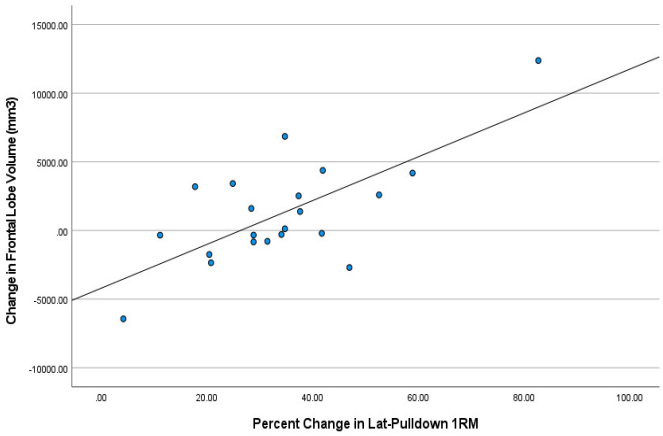
**Sarah Cooley**[1], Brittany Nelson[1], Alexander Rosenow[1], Beau M. Ances[1]
*[1]Washington University in St Louis, St Louis, MO, USA*

**Background:** Exercise intervention programs have been associated with improved brain integrity in people living without HIV; however, the effects of exercise on brain integrity in people living with HIV (PLWH) has not been well-studied. The current study examined changes in cognition, brain volumes and inflammatory markers in a cohort of older PLWH who completed a six-month exercise intervention.

**Methods:** A total of 30 (≥50 years old), virologically well-controlled (<50 copies/mL) PLWH (76% male) completed an exercise intervention program, cognitive testing, blood draw, and a magnetic resonance imaging (MRI) scan. Participants completed gym sessions three times a week for six months with a personal trainer on site. Cognitive testing, blood draw (to calculate plasma soluble CD14 (sCD14)), and the MRI scan to calculate brain volumes were completed both at a baseline session and after the six-month exercise intervention. A one-repetition maximum (1RM), the highest weight a participant could lift for one successful repetition, was assessed for four strength exercises (leg press, chest press, latissimus dorsi (lat) pull-down, and seated row) at baseline and six-month follow-up. Analyses examined the percent change in 1RMs over time, and associations between changes in strength, cognitive performance, brain volumes, and sCD14.

**Results:** The 1RM of all four strength exercises significantly increased over time for all participants (p-values <.001). Greater increases in the lat pull-down exercise were significantly associated with better executive function performance (p=.04), and greater volumes in cortex (p=.001), cortical white matter (p=.03), total gray matter (p=.003), frontal lobe (p<.001) (Figure 1), parietal (p=.02), temporal (p=.01), and cingulate (p<.001) volumes. Greater increases in chest press 1RM were significantly associated with greater thalamic volume (p=.01). Additionally, greater decreases in sCD14 over time were significantly related to greater increases in lat pull-down (p=.02), seated row (p<.001), and chest press (p=.002) 1RM.

**Conclusion:** Exercise and improving physical strength represents an easily modifiable behavior that may be beneficial in improving brain integrity and reducing inflammation in older PLWH. Longer studies with a greater number of participants, particularly female PLWH, are needed to more fully understand these relationships.




## 421 MACHINE LEARNING QUANTIFIES ACCELERATED WHITE MATTER AGING IN PERSONS WITH HIV

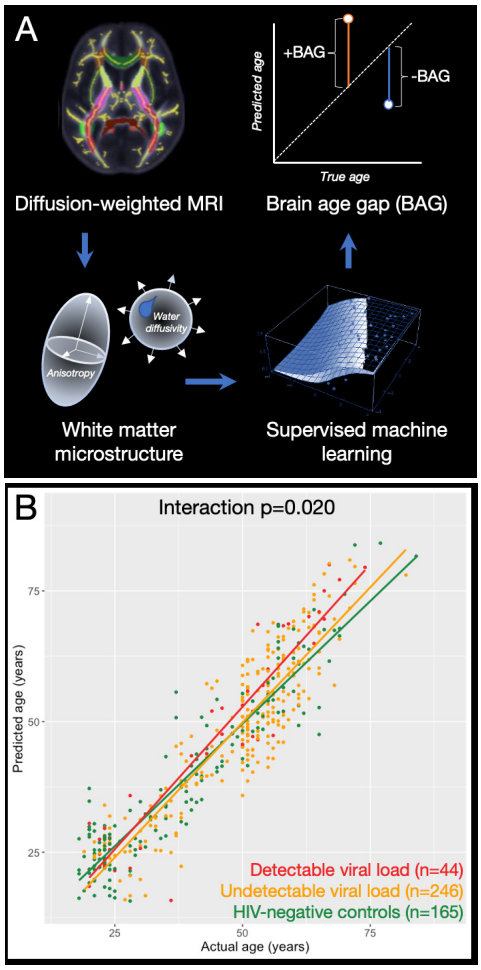
**Kalen Petersen**[1], Jeremy Strain[1], Sarah Cooley[1], Florin Vaida[2], Beau M. Ances[1]
*[1]Washington University in St Louis, St Louis, MO, USA, [2]University of California San Diego, San Diego, CA, USA*

**Background:** Older persons with HIV (PWH) undergo pathological changes to cerebral white matter, detectable on diffusion-weighted MRI. These changes can be quantified using the brain age gap (BAG), the difference between true age and neuroimaging-predicted 'brain age.' It is hypothesized that white matter aging, i.e. progressive accumulation of microstructural damage, is accelerated in PWH with detectable viral load. However, other risk factors for white matter aging remain uncertain.

**Methods:** 290 PWH (age=48.2±13.7 yr.; 23% female; 65% African-American; 85% virally suppressed) and 165 HIV- controls (age=37.5±16.3 yr.; 47% F; 56% A.A.) provided informed consent and were imaged at a single site. Age, race, and sex were co-variates in all analyses. Diffusion MRI was performed on a 3-Tesla Siemens scanner (TR/TE=9100/104ms, resolution=2x2x2mm, gradient directions=30). Potential correlates of HIV severity and white matter aging were quantified: plasma viral load, current CD4+ lymphocytes, nadir CD4+, hepatitis C, body-mass index, 10-year Framingham cardiovascular risk score, and global cognitive z-score. A Gaussian process regression model was trained to predict age from diffusion MRI scalars (diffusivity and fractional anisotropy) using 624 publicly available healthy controls from the Cambridge Center for Aging and Neuroscience. The trained model was then applied to this cohort to quantify BAG (Panel A). To test for accelerated white matter aging, BAG was modeled as an interaction between viral load and age. Potential risk factors for white matter aging were identified using generalized linear regression with backwards variable selection and a stop criterion of p<0.10.

**Results:** The trained machine learning model predicted age in previously unseen participants with a mean absolute error of 5.3 years after linear de-trending (R2=0.48; p<0.001). Age and viral load (>50 copies/mL) had a significant interactive effect on BAG, such that PWH with detectable viral load accumulated +1.5 years of additional BAG per decade vs. HIV- controls (p=0.020; Panel B). Backwards selection identified two features associated with advanced white matter aging: greater 10-year Framingham risk score (p=0.002) and lower global cognitive z-score (p=0.043).

**Conclusion:** Aging with detectable plasma HIV and elevated cardiovascular risk are significant correlates and potential risk factors for white matter pathology, and may contribute to the etiology of cognitive impairment in PWH.




## 422 ASSESSING HEALTH-RELATED QUALITY OF LIFE IN PEOPLE WITH HIV AND COGNITIVE ISSUES

New Investigator Scholar

**Kate Alford**[1], Stephanie Daley[1], Sube Banerjee[2], Elizabeth Hamlyn[3], Daniel Trotman[3], Jaime Vera[1]

*[1]Brighton and Sussex Medical School, Brighton, UK, [2]University of Plymouth, Plymouth, UK, [3]King's College Hospital, London, UK*

**Background:** We selected and examined a comprehensive set of domains measures that capture health-related quality of life (HRQoL) in people living with HIV and cognitive issues. This allows clinicians to target care to address the factors driving HRQoL, focus care on individual needs, follow changes over time, and quantify interventions.

**Methods:** HIV patients with subjective cognitive concerns (based on European AIDS Clinical Society guidelines) were identified from two clinics in London and Brighton (UK) and invited to complete a brief cognitive assessment (MoCA-Blind) and an in-person or online series of validated questionnaires measuring nine domains identified from a prior qualitative study as comprising HRQoL in PLWH with cognitive impairments. These included: physical function (Lawson and Brody Instrumental Activities of Daily Living), cognition (MoCA-Blind), social connectedness (Social Connectedness Scale), physical and mental health and wellbeing (SF-12), HIV stigma (Stigma Scale for Chronic Illness), self-esteem (Rosenburg's Self-Esteem Scale), acceptance of health (Acceptance of Illness Scale) and control over health outcomes (Illness Perception Scale).

**Results:** 103 PLWH with cognitive concerns (Male = 93, 90.3%) showed that the questionnaires selected had good internal consistencies and exploratory factor analysis revealed that domain total scores load onto one main factor, representing HRQoL. Most domains were significantly correlated (r's 0.28 to -0.74, $p < 0.05$) in expected directions. We explored cut-off scores which revealed a significant proportion of patients scored outside the desired range on single domains (between 33 and 79.6%), and many patients on multiple domains (40.8% on 4 or more domains). Multiple regression revealed presence of objective cognitive impairment (based on MoCA-Blind cut-off score ≤ 18) significantly predicted HRQoL score ($R^2 = 0.14$, $F(1, 91) = 15.15$, $p < 0.001$), and adding the remaining HRQoL domains explained 56% of the variance in HRQoL score ($R^2$ of 0.56, $\Delta R^2 = 0.41$ $F(8,83) = 11.76$, $p < 0.001$).

**Conclusion:** HRQoL for the majority of PLWH with cognitive issues could be improved and we have succeeded in identifying important domains driving these experiences. The domains were strongly associated with one another, therefore insights into any could inform interventions to improve HRQoL. This provides targets for intervention development and clinical consultation to maintain or improve HRQoL in PLWH with cognitive issues.

## 423 PRESCRIBED DRUGS DISTINGUISH DATA-DRIVEN COGNITIVE PROFILES IN PEOPLE WITH HIV (PWH)

**Raha Dastgheyb**[1], Yanxun Xu[1], Alison Buchholz[1], Donald Franklin[2], Ronald J. Ellis[2], Susan Morgello[3], David Clifford[4], Benjamin B. Gelman[5], Christina M. Marra[6], Robert K. Heaton[2], David J. Moore[2], Scott L. Letendre[2], Qing Ma[7], Leah H. Rubin[1]

*[1]The Johns Hopkins University, Baltimore, MD, USA, [2]University of California San Diego, La Jolla, CA, USA, [3]Mt Sinai School of Medicine, New York, NY, USA, [4]Washington University in St Louis, St Louis, MO, USA, [5]University of Texas at Galveston, Galveston, TX, USA, [6]University of Washington, Seattle, WA, USA, [7]University at Buffalo, Buffalo, NY, USA*

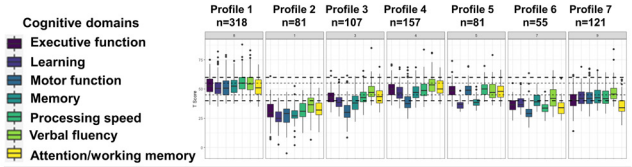
**Background:** PWH have more age-associated medical and psychiatric comorbidities than the general population, even when treated with antiretroviral therapy (ART). These comorbidities have been associated with poorer cognition, but less is known about the cognitive effects of the treating medications.

**Methods:** We leveraged cross-sectional data collected between 2015-2019 from 920 virally-suppressed PWH enrolled in CHARTER, NNTC, or UCSD neuroHIV cohorts with available count data on 226 non-ART drug classes gathered contemporaneously with comprehensive neuropsychological testing. A principal components analysis (PCA) reduced the drug classes to 16 components that were then manually named based on highest loading drug categories. To identify subgroups of PWH with similar cognitive deficit profiles, we used a pipeline consisting of dimension reduction with Self-Organizing Maps on domain-specific cognitive deficit scores to focus followed by clustering using Gaussian mixture models, and the number of clusters was identified using Entropy. We next created Random Forest (RF) models to determine the degree to which the PC drug classes distinguished cognitive profiles, along with sociodemographics and comorbidities. RF models contained an ensemble of 1000 trees with a 70/30 training/testing set for validation. Model performance was evaluated based on metrics, and the models with a receiver operating characteristic value of ≥0.65 were further evaluated with variable Importance measures to identify the top 10 contributing variables.

**Results:** PWH had a median age of 56 years (IQR:50-64) and were mostly white (58%) males (69%). The median number of non-ART drugs was 6 (IQR:3-10). Among PWH, 10 cognitive profiles were identified, including an unimpaired one. Drug class PCs had adequate utility differentiating 6 profiles from the unimpaired profile (Figure). PC1 (CNS agents) differentiated 3 of 6 profiles from the unimpaired one. Other PCs differentiating profiles included autonomic, metabolic/endocrine, and renal/antihypertensive drugs.

**Conclusion:** Different combinations of drug classes were associated with different cognitive profiles, suggesting that the drug combinations may differently affect underlying neurobiological pathways. Further investigation is needed to account for the underlying conditions for which the drugs were prescribed and to understand the risks/benefits associated with different drug combinations and cognition in PWH.

**Figure**. The top part (and Table columns) indicate six (Profiles 2-7) of the 10 cognitively weak-to-severe impairment profiles and the unimpaired cognitive profile (Profile 1) identified among virally suppressed PWH on ART that were adequately predicted by the machine learning algorithms. The bottom part indicates the top 10 variables that distinguished each of the cognitive weak-to-severe impairment profiles from the unimpaired cognitive profile.




| Factor Number: Factor Name | Profile 2 | Profile 3 | Profile 4 | Profile 5 | Profile 6 | Profile 7 |
|---|---|---|---|---|---|---|
| **PC1: CNS agents** | • | • | • | | | |
| **PC2: EENT/hormones** | | | | | • | |
| **PC5: Miscellaneous** | | | • | | • | |
| **PC6: Metabolic** | | | • | | • | |
| **PC7: Antimicrobials** | | | | | | • |
| **PC8: Autonomic drugs** | | | • | | | |
| **PC10: Vitamin supplements** | | | | | • | |
| **PC12: Renal agents** | • | | | | | • |
| Enrollment site | • | | | | | • |
| Years of education | | | | | | • |
| Race (white, black, other) | • | | | • | | |
| WRAT-4 Reading subtest | | | | | | • |
| Beck Depression Inventory-II | | • | | | | |
| Nadir CD4 | • | | | | | |
| CD8 absolute | | • | | | | |
| CD4/CD8 ratio | | • | | | | |
| ART status | | | | • | | |
| Months of total ART exposure | • | | | | • | |
| Total number of ART drugs on | | | | • | | |
| Body mass index | • | | | • | | • |
| Cerebrovascular accident | | | | | | • |
| Lifetime cannabis use disorder | | | | | | • |
| Total # of non-ART medications | | • | | | • | |
| Lifetime hallucinogen disorder | | | • | | | |

Note: "Weak"=T score 40-49. "Impaired"= T score<40. Impairment ranges: mild: 35-39, mild to moderate: 30-34, moderate:25-29, moderate-to-severe: 20-24, severe: <20; EENT=ear, eyes, nose, and throat; WRAT-4: Wide Range Achievement Test-4

**Profile Labels** :1. Unimpaired, 2. Mild-to-moderate impairment across domains, 3. Mild-to-moderately impaired motor, mildly impaired learning and recall, and weak processing speed, working memory, and executive functioning, 4. Weak motor, 5. Mildly impaired learning and recall, 6. Mild-to-moderately impaired motor and processing speed, mildly impaired working memory, learning, and executive functioning, and weak recall and verbal fluency, 7. Mildly impaired working memory and weak motor, processing speed, executive functioning, learning, and recall

114 sociodemographic, clinical, behavioral, immunohistochemistry variables were included the in random forest modelling. Here we only depict comorbidities that remained among the top predictors

## 424 PREVALENCE AND CHARACTERISTICS OF HIV-ASSOCIATED STROKE IN A SOUTH AFRICAN SETTING

**Craig Corbett**[1], Naeem Brey[2], Richard D. Pitcher[2], Suzanne O'Hagan[2], Tonya M. Esterhuizen[1], Felicia C. Chow[3], Eric Decloedt[1]
*[1]Stellenbosch University, Tygerberg, South Africa, [2]Tygerberg Hospital, Cape Town, South Africa, [3]University of California San Francisco, San Francisco, CA, USA*

**Background:** Antiretroviral treatment (ART) era HIV-associated stroke data from Sub-Saharan Africa is limited. We determined the prevalence of HIV in patients presenting with acute symptomatic stroke, and compared risk factors, clinical characteristics, and brain imaging with age-matched stroke patients without HIV.

**Methods:** We conducted a retrospective study of adults presenting with any type of stroke to Tygerberg Hospital in a 12-month period. Patients living with HIV (PLWH) and HIV-uninfected patients (HIV-) were matched on age group (1:2 ratio). Patients were identified by keyword search, while HIV status was ascertained from laboratory data. Clinical and imaging data were extracted from medical records.

**Results:** Among 884 patients presenting with acute strokes, the prevalence of HIV infection was 9.3% (95% CI: 7.4-11.2%), with 496 patients (56.1%) with negative HIV status and 306 patients with unknown HIV status (34.6%). Mean age at presentation in PLWH was 46 (± 11) years compared to 55 (± 14) years in HIV- (p<0.001). Hypertension and dyslipidaemia were less prevalent in PLWH (hypertension: 53.7% vs 70.1%, p=0.011; dyslipidaemia: 13.4% vs 29.9%, p=0.005). Concurrent infection was more prevalent in PLWH (25.6% vs 4.9%, p=<0.001), largely in patients with CD4 count <200 cells/mcL. PLWH with higher CD4 counts (≥200 cells/mcL, 51.3%) had more traditional risk factors and less concurrent infection. Among PLWH, 68.3% were on ART, and 39.3% of these had been started or restarted on ART within the past 6-months. Basal ganglia infarcts (35.6% vs 18.3%, p=0.014) and multiple vascular territory involvement (25.4% vs 7.7%, p=0.002) was more common in PLWH. Clinical presentation, ischaemic stroke type, and in-hospital outcomes did not differ between groups.

**Conclusion:** Stroke patients with HIV were younger, had less traditional cardiovascular risk factors, and more concurrent infections than patients without HIV, especially those with a lower CD4 count. Recent ART initiation or reinitiation rates were high. Significant differences in CT brain imaging findings were seen. Understanding the multifactorial mechanisms underlying increased stroke risk, including associated infections and potential ART-associated immune reconstitution, is crucial and needs further study.

## 425 ABNORMAL COGNITIVE AGING IS DETECTED DESPITE CLINICALLY DEFINED COGNITIVE STABILITY

New Investigator Scholar

**Htein Linn Aung**[1], Thomas Gates[1], Limin Mao[2], Bruce Brew[1], Krista J. Siefried[1], Andrew Carr[1], Lucette A. Cysique[1]
*[1]St Vincent's Centre for Applied Medical Research, Sydney, Australia, [2]University of New South Wales, Sydney, Australia*

**Background:** Australia has surpassed the UNAIDS targets of 90% ART coverage and viral suppression among treated people living with HIV (PLHIV). This national HIV treatment success provides us with a unique context to study cognitive trajectories, cognitive aging, and a comprehensive set of health, social and lifestyle factors that may influence cognition during chronic and stable HIV disease.

**Methods:** The Predictors of Adherence to Antiretroviral Therapy (PAART) study recruited 523 PLHIV (median age=52) with undetectable plasma HIV RNA (<50 copies/mL) in the 3 months prior to enrolment from 17 HIV treatment facilities in Australia. Participants were followed-up annually for 2 years. A total of 457 participants at baseline, 316 at Month 12, and 276 at Month 24 completed cognitive screening: CogState Computerized Battery (CCB). Demographics, socioeconomic factors, healthcare-seeking behaviors, lifestyle factors, HIV disease variables, physical and mental health status, and comorbidities were assessed. The CCB data were corrected for age, education, sex, and practice effect and averaged into a global z-score (GZS). Clinically relevant cognitive trajectories (decline, stability, and improvement) were defined using linear mixed-effect regression (LMER)-based GZS change scores (i.e., within or +/- 90% CI). A LMER model with a top-down variable selection approach identified the independent effects of age and other demographic, socioeconomic and health-related factors on the GZS.

**Results:** Cognitive decline was seen in 6% at Month 12 and 7% at Month 24; 3% improved at both time points. In the LMER model with GZS as the outcome, interaction between older age (>50 years) and follow-up time was associated with lower GZS (β=-0.31, CI=-0.39, -0.22, P=<0.001). Having a regular relationship (β=0.14, CI=0.00, 0.28, P=<0.05), excellent English proficiency (β=0.22, CI=0.04, 0.41, P=<0.05), and perceived stigma (avoidance) due to HIV status (β=0.15, CI=0.01, 0.30, P=<0.05) were associated with better GZS. Relying on government subsidy (β=-0.27, CI=-0.52, -0.03, P=<0.05), severe depression (β=-0.28, CI=-0.53, -0.03, P=<0.05), and lower belief in ART necessity and acceptability (β=-0.09, CI=-0.16, -0.02, P=<0.05) were associated with poorer GZS.

**Conclusion:** In this large nationally representative cohort of virally suppressed PLHIV, while clinically relevant cognitive stability is common, we detected a medium abnormal aging effect, and complex impact of psycho-socio-economic factors on longitudinal cognitive performance.

*Table 1: Variables used in the final linear mixed-effect regression model to identify the factors associated with longitudinal cognitive performance*

| Category | Variables |
|---|---|
| Aging | Age group (<50 VS ≥50), Age group (Young VS Old) * Follow-up time (Year) |
| Demographics | Gender (Female VS Male), Homosexual (Yes), Excellent English (Yes), Eligible for Medicare (Yes), Completed Year 12 (Yes) |
| Socioeconomic factors | In a regular relationship (Yes), Government subsidy as the main source of income (Yes), Received financial assistance in the last 12 months (Yes), Employed (Yes) |
| Lift-style factors | Alcohol use in the past 12 months (Yes), Smoking at least once a week in the past 12 months (Yes), Use a drug at least once a week in the past 12 months (Yes) |
| Mental health | Severe Depression a (Yes), More than 2 major stress events in previous 12 months (Yes), History of psychiatric disorder (Yes) |
| Physical health | Self-perceived health status (Poor/Average VS Good/Very Good), Hospital admission in the last 12 months (Yes) |
| Stigma | Has disclosed HIV status to someone (Yes), Has felt avoided, excluded, or rejected for having HIV (Yes), Has had awkward interactions for having HIV (Yes) |
| HIV-related | Simplified Medication Adherence Questionnaire score, Missed antiretroviral treatment at least once in the past three months (Yes), Belief in necessity and acceptability of antiretroviral treatment score (mean, SD), Historical AIDS (Yes), HIV brain involvement history (Yes), Duration of living with HIV (Year) |
| Comorbidities | Normal alanine aminotransferase (Yes), History of Syphilis (Yes), Other comorbidity (Yes), Hypertension (Yes), Diabetes (Yes), History of Hepatitis C Virus infection (Yes) |

## 426 COGNITIVE PREDICTORS OF EVERYDAY FUNCTIONING IN THE WOMEN'S INTERAGENCY HIV STUDY

**David Vance**[1], Pauline Maki[2], Danyang Yu[3], Raha Dastgheyb[4], Gayle Springer[5], Kathryn Anastos[6], Deborah Gustafson[7], Kathleen Weber[8], Derek M. Dykxhoorn[9],

Joel Milam[10], Monica M. Diaz[11], Seble Kassaye[12], Drenna Waldrop[13], Yanxun Xu[4], Leah H. Rubin[4]
*[1]University of Alabama at Birmingham, Birmingham, AL, USA, [2]University of Illinois at Chicago, Chicago, IL, USA, [3]The Johns Hopkins University, Baltimore, MD, USA, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]John H Stroger Jr Hospital of Cook County, Chicago, IL, USA, [6]Albert Einstein College of Medicine, Bronx, NY, USA, [7]State University of New York Downstate Medical Center Downstate Medical Center, Brooklyn, NY, USA, [8]Cook County Health & Hospitals System, Chicago, IL, USA, [9]University of Miami, Miami, FL, USA, [10]University of California Irvine, Irvine, CA, USA, [11]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [12]Georgetown University Medical Center, Washington, DC, USA, [13]Emory University, Atlanta, GA, USA*

**Background:** Nearly 30% of people with HIV experience an impairment of cognition that can interfere with performing instrumental activities of daily living (IADL). We examined cognitive performance in women with HIV (WWH) and HIV-uninfected women from the Women's Interagency HIV Study (WIHS) to determine the relationship between cognitive function across seven cognitive domains and self-reported IADL.
**Methods:** Cognitive performance across 7 domains and the Lawton and Brody IADL scale were assessed in WWH and HIV-uninfected women from the WIHS. A series of weighted logistic mixed effect models were conducted to examine associations between cognitive performance and functional outcomes (IADL total score and item level scores). Models were conducted in the overall sample (WWH + HIV-uninfected), WWH only, Virally Suppressed (VS)-WWH, and HIV-uninfected women.
**Results:** There were 2,025 participants in the sample including 1,320 WWH (85% VS, 57% >50 years of age) and 617 HIV-uninfected women (50% >50 years of age). Among all participants, motor function was the main cognitive domain showing an impaired IADL. Poorer motor function was associated with poorer function in getting where you need to go (P<0.001), dressing (P=0.001), home repairs (P<0.001), housekeeping (P<0.001), cooking (P=0.001), and laundry (P<0.001). In women <50 years (younger), poorer motor function was associated with poorer function in getting where you need to go (P=0.007), cooking (P=0.003), and home repairs (P=0.009). In women >50 years, motor function was associated with poorer function in getting where you need to go (P=0.006), home repairs (P=0.001), housekeeping (P=0.003), and laundry (P=0.002). Among WWH, poorer motor function was associated with poorer function in dressing (P=0.01), home repairs (P<0.001), housekeeping (P=0.001), and laundry (P=0.009), and was driven by older WWH. Moreover, poorer executive function was associated with reduced ability to plan social activities (P=0.007). There were no associations between motor function and IADLs among younger WWH. Among all VS-WWH, motor function was associated with difficulty completing home repairs (P<0.001) only. In HIV-uninfected women, motor function was the only domain associated with IADLs.
**Conclusion:** Since motor and executive performance were related to poorer function in certain IADLs, strategies such as domain-specific cognitive training could improve everyday functioning.

## 427 A NOVEL COMORBIDITY INDEX PREDICTS COGNITIVE CHANGE IN PEOPLE WITH CHRONIC HIV

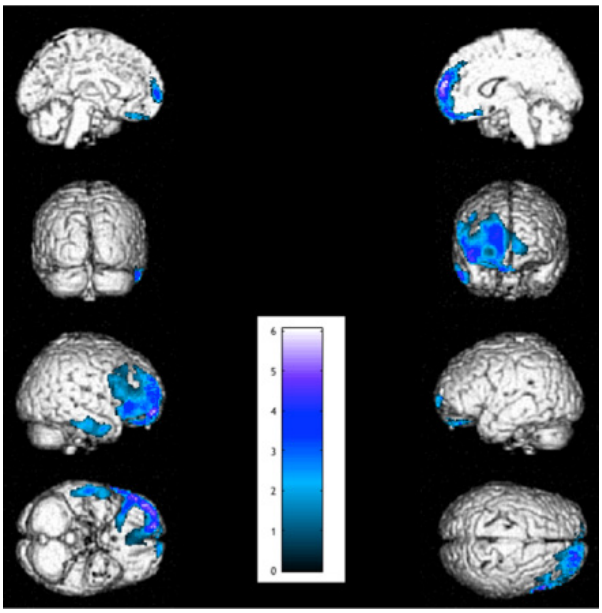
**Ronald J. Ellis**[1], Bin Tang[1], Sara Gianella[1], Christina M. Marra[1], David Clifford[2], Igor Grant[1], Benjamin B. Gelman[3], Susan Morgello[4], J. Allen McCutchan[5], Scott L. Letendre[1], Robert K. Heaton[1]
*[1]University of California San Diego, San Diego, CA, USA, [2]Washington University in St Louis, St Louis, MO, USA, [3]University of Texas Medical Branch, Galveston, TX, USA, [4]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [5]University of California San Diego, La Jolla, CA, USA*

**Background:** People with chronic HIV (PWCH) have an excess burden of comorbidities with a substantial adverse impact on mortality and quality of life. But their effects on long-term neurocognitive (NC) outcomes are less well-studied.
**Methods:** Inclusions: people with HIV for at least 2 years. Exclusions: active conditions sufficiently severe to interfere with the study evaluations. We constructed a simple comorbidity index (SCI, one point per comorbidity, range 0-5), selected based on univariable analyses predicting neurocognitive decline over 12 years, comprising the presence or absence of diabetes, hypertension, neuropathic pain, chronic obstructive pulmonary disease (COPD), and current major depressive disorder (MDD). Linear regression assessed the relationship between the SCI and a published, summary regression-based change score (sRBCS), adjusted for baseline, practice effect, and other factors, measuring change in overall NC performance. We compared the SCI to other well-established comorbidity indices: The Charlson, Veterans Administration Comorbidity Score (VACS) and Framingham cardiovascular risk.
**Results:** Participants were 397 PWCH enrolled between 2003-2009, mean (SD) age at baseline 43.5 (7.68) years, 304 (76.6%) men, 164 (41.3%) white, education 13.0 (2.63) years, median (interquartile range, IQR) estimated duration of HIV 9.82 (4.44, 14.5), nadir and current CD4+ T-lymphocytes/uL 172 (30, 308) and 452 (278, 636), On ART 74.3%, 45.9% with undetectable plasma HIV RNA. Those with higher SCI at baseline had significantly worse cognitive change over 12 years (p=0.003, R2=0.03). There was a dose-response relationship such that those with 3 baseline comorbidities had worse decline than those with 2, 2 worse than 1, and 1 worse than none (indices of 2+ and 1 vs. none, effect sizes 0.64 and 0.29). SCI was significantly associated with declines in the specific domains of executive function, learning, verbal, and SIP. In separate multivariable models using previously published indexes (Charlson, VACS and Framingham CVD risk), only the SCI was significantly associated with NC worsening rate. Comorbidities with the largest effects at baseline were hypertension, COPD and current MDD.
**Conclusion:** Baseline comorbidities in PWCH predicted subsequent trajectories of global cognitive decline over extended follow-up, suggesting that any treatments for these comorbidities during the follow-up period were only partly effective, and that more successful treatment of them might ameliorate NC decline.

## 428 RECREATIVE DRUGS: NEW SUSPECTS IN HAND MYSTERY GAME

**Sophie Henrard**[1], Nicola Trotta[1], Antonin Rovai[1], Tim Coolen[1], Hichem Slama[1], Jean-Christophe Goffard[1], Serge Goldman[1], Xavier De Tiège[1]
*[1]Hôpital Universitaire Erasme, Brussels, Belgium*

**Background:** Despite the high prevalence of HIV associated neurocognitive disorder (HAND), its pathogenesis remains unclear and efficient diagnostic tools are lacking. This study characterizes the structural and metabolic cerebral correlates of HAND in a preclinical setting that considers the lifestyle of young European men having sex with men.
**Methods:** Structural brain magnetic resonance imaging (MRI) and positron emission tomography with [18F]-fluorodeoxyglucose (FDG-PET) were prospectively acquired simultaneously on a hybrid PET-MR in 23 young asymptomatic HIV+ men with a normal CD4+ cell count and undetectable viral load; 26 men HIV negative pre-exposure prophylaxis users (HIV-PrEP), highly well matched for what concerns lifestyle and age; and in 23 matched healthy young men from the general population (HC). FDG-PET data were analyzed using a voxel-based approach. Structural MRI data were analyzed using atlas-based brain parcellisation. A comprehensive neuropsychological assessment and a recreative drug use survey were also administered to the HIV+ and HIV-PrEP groups for further correlation analysis.
**Results:** Both HIV+ and HIV-PrEP subjects exhibited asymptomatic neurocognitive impairment (ANI) based on Frascati's criteria. HIV+ had lower performances in executive functions, attentional and working memory functions compared to HIV-PrEP. No structural or metabolic brain difference was observed between HIV+ and HIV-PrEP subjects. Compared with HC, HIV+ and HIV-PrEP subjects displayed significant hypometabolism in the right dorsolateral and dorso-mesial prefrontal cortex (see figure) that correlated to the level of recreational drug use but not with the level of dysexecutive deficits.
**Conclusion:** ANI based on Frascati's criteria is not specific of HIV+ subjects but is also observed, to a smaller extent, in HIV-PrEP subjects. Prefrontal hypometabolism in the absence of brain atrophy was similar in those populations and was related to the use of recreational drugs use. A dynamic prevention of recreative drugs use in those populations is therefore mandatory to cope with their negative impact on brain function and their neurocognitive consequences. A complex interplay between recreative drugs and HIV is probably involved in the induction and development of HAND in young HIV+ men.



## 429 IV PUSH ADMINISTRATION OF IBALIZUMAB: PHARMACOKINETICS, SAFETY, AND EFFICACY

**Edwin DeJesus**[1], Gary Richmond[2], Mezgebe Berhe[3], Anthony Mills[4], Tanya Schreibman[5], Charlotte-Paige Rolle[1], Kuei-Ling Kuo[6], Mohammed Zogheib[7], Olivia G. Goss[7], Robert B. Cash[8], YingAn Lai[6], Martin Markowitz[9], Pedro M. Mesquita[8]

*[1]Orlando Immunology Center, Orlando, FL, USA, [2]Broward Health Medical Center, Fort Lauderdale, FL, USA, [3]North Texas Infectious Diseases Consultants, Dallas, TX, USA, [4]Men's Health Foundation, Los Angeles, CA, USA, [5]CAN Community Health, Sarasota, FL, USA, [6]TaiMed Biologics Inc, Taipei City, Taiwan, [7]Syneos Health, Somerset, NJ, USA, [8]Theratechnologies, Inc, Montreal, Canada, [9]Columbia University, New York, NY, USA*

**Background:** Ibalizumab (IBA) is a long-acting post-attachment inhibitor approved for the treatment of multi-drug resistant HIV-1 infection in heavily treatment-experienced (HTE) adults. IBA is diluted in 250 mL of saline and administered via intravenous infusion (IVI) as a loading dose of 2000 mg followed by 800 mg maintenance doses, every 2 weeks. We sought to evaluate administration of IBA maintenance doses as undiluted IV push (IVP) over 30 seconds (s).

**Methods:** In TMB-302, an open-label non-randomized Phase III study, clinically stable people with HIV (PWH) on IBA-containing ARV regimens and HIV-uninfected individuals (UI) were administered IBA at progressively increasing concentrations over shortening intervals and then as IVP. Blood samples were collected at various times pre- and post-dosing via IVI and IVP to estimate PK parameters. A PK bridge between IVI and IVP was demonstrated if the proportion of subjects with IBA serum trough concentrations ($C_{trough}$) ≥ 300 ng/mL was comparable by two one-sided tests of significance (TOST), and the 90% confidence interval (CI) of area under the curve (AUC) geometric mean ratios was within 0.80-1.25. All subjects were followed for safety throughout and monitored for development of anti-drug antibodies (ADA). IBA efficacy was assessed in PWH by measuring viral load (VL).

**Results:** A total of 22 subjects, 9 HIV+ and 13 HIV-, predominantly male (81.8%) and white (95.5%) were enrolled. All PWH and 10/13 UI completed the study. Reasons for discontinuation were: adverse events (AEs) unrelated to IBA, consent withdrawal and protocol noncompliance. The proportion of subjects with average $C_{trough}$ ≥ 300 ng/mL was 18/19 (94.7%) for both IVI and IVP and the 90% CI of the AUC ratio of IVP to IV Infusion was within the target value (0.9478-1.1226). Among PWH, median VL at baseline and end of study was <20 copies/mL, with no virologic failures observed. One subject experienced virologic rebound following the last IVP dose, which was linked to non-adherence to the oral antiretroviral regimen. All AEs were mild to moderate, with no serious AEs recorded and ADA were not detected for any subjects.

**Conclusion:** Administration of IBA as an undiluted IVP over 30s was safe and well tolerated in all participants, and remained effective among PWH. Bioequivalence between IVI and IVP administration was demonstrated and supports IVP as a potential alternative for delivery of IBA. Assessment of IM injection as an additional option for HTE patients is ongoing in this study.

## 430 DEEPHIV: DEEP LEARNING TO PREDICT DDI RELEVANCE FOR ARVs

**Thao Pham**[1], Mohamed Ghafoor[2], Justin Chiong[1], Dennis Wang[3], Marco Siccardi[1]

*[1]University of Liverpool, Liverpool, UK, [2]University of Liverpool, Liverpool, UK, [3]Sheffield University, Sheffield, UK*

**Background:** Drug-drug interaction (DDI) represents an important element complicating the clinical and pharmacological management of the antiretroviral therapy. Due to the high number of possible drug combinations, a limited number of DDI studies are conducted, cannot be ethically studied, and DDIs have an impact on different phases of drug development. Deep learning, a type of artificial intelligence (AI) inspired by the human neural network, offers a powerful tool to predict DDI magnitude and related risk considering large number of drug combinations. The aim of this study was to develop a deep learning algorithm, called DeepHIV, to predict DDI risk between antiretrovirals (ARV) and comedications.

**Methods:** The dataset was provided by the Liverpool HIV Drug Interaction database (https://www.hiv-druginteractions.org/). Molecular structure of each drug was converted to Morgan fingerprints where each atom was represented in numerical format. A mathematical framework was applied to compare the fingerprints, constructing drug similarity profiles. The architecture of DeepHIV was a feed-forward neural network where drug similarity profiles were fed into the input layer. 28,026 drug pairs were split to 80% for training and 20% for testing. DeepHIV was trained to predict 3 classes of DDI: i) Red: drugs should not be co-administered, ii) Amber: potential interaction may require close monitoring and iii) Green: no clinically significant interaction.

**Results:** The performance of DeepHIV on the test set (5,824 pairs) achieved 85% mean accuracy, 70% mean precision, 69% mean sensitivity, and 84% mean specificity. A confusion matrix, which is a summary of prediction results versus the actual DDIs, was shown in Figure 1A. DeepHIV was utilised to predict DDI magnitude between first-line ARVs and comedications, which were composed of 687 drugs. The overall performance on first-line ARVs was above 80% accuracy and 70% sensitivity (Figure 1B).

**Conclusion:** DeepHIV predicts clinical and pharmacological relevant DDI between ARVs and comedication with a mean accuracy of 85%. The deep learning approach was developed exclusively integrating molecular data and provides a comprehensive evaluation of ARV DDIs. The algorithm represents a predictive tool to rationalise the risk related to DDI and delineates opportunities for a strategical integration of AI approaches during the development of novel therapies as well the identification and design of clinical studies.

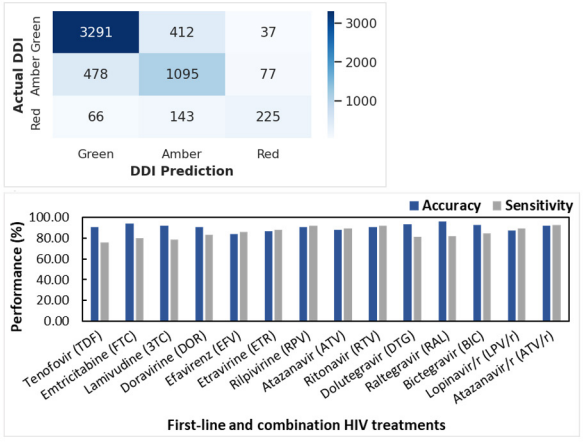



**Figure 1. The performance of DeepHIV on the test set and first-line ARVs. A)** Confusion matrix of DDI prediction versus actual DDI on the test set of 5,824 drug pairs. **B)** DeepHIV predicted DDI between first-line ARVs and all 687 drugs (comedications) available on the dataset, evaluation metrics were shown as accuracy and sensitivity.

## 431 PK & SAFETY OF DARUNAVIR/COBICISTAT WITH ONCE-WEEKLY ISONIAZID/RIFAPENTINE

**Kristina M. Brooks**[1], Alice K. Pau[2], Doris Swaim[3], Haden T. Bunn[1], Lilian Adeojo[1], Charles A. Peloquin[4], Parag Kumar[1], Joseph A. Kovacs[1], Jomy M. George[1]
*[1]National Institutes of Health Clinical Center, Bethesda, MD, USA, [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [3]Leidos Biomedical Research, Inc, Frederick, MD, USA, [4]University of Florida, Gainesville, FL, USA*

**Background:** Once-weekly isoniazid (INH) with rifapentine (RPT) for 3 months (3HP) is a recommended treatment for latent tuberculosis infection (LTBI) in PWH. Drug-drug interactions between 3HP and ARVs are of concern, notably subtherapeutic ARV exposures due to induction by RPT, resulting in limited options for the concomitant use of 3HP with ARVs. Here we examined the pharmacokinetics (PK) and safety of DRV/c when coadministered with 3HP. We hypothesized that DRV exposures would be decreased with 3HP coadministration.

**Methods:** This was an open-label, fixed sequence, 2-period crossover study in healthy volunteers. Participants received DRV/c 800 mg/150 mg once-daily alone for 4 days, then continued DRV/c once-daily for Days 5-19 with weekly 3HP coadministration on Days 5, 12, and 19. Intensive PK assessments were performed over 24 hours on Days 4 (DRV/c alone), 14 (DRV/c 48-72 hours after 3HP), and 19 (DRV/c simultaneously with 3HP). PK parameters were determined using noncompartmental methods (Phoenix WinNonlin). Geometric mean ratios (GMR) with 90% confidence intervals (CIs) were calculated and compared between phases using mixed effects models.

**Results:** A total of 13 participants were enrolled (10 males; 8 white, 3 black, 2 others; 2 Hispanic/Latino; median [range] age 25 [21-45] years and weight 70.7 [62-85.1] kg). PK results are summarized in the Table. Relative to DRV/c alone, DRV AUC0-24h, C0h, $C_{max}$, and C24h were significantly decreased with 3HP coadministration, with more marked decreases ~48-72 hours after RPT administration (Day 14) in comparison to simultaneous administration (Day 19). CLss/F was increased and V/F differed depending on the timing of 3HP administration, suggesting induction and changes in bioavailability, respectively, with 3HP. On Day 14, several individual C0h (6/13) and C24h (8/13) were below the DRV $EC_{50}$ (0.055 ug/mL). On Day 19, 0/10 C0h and 1/10 C24h fell below the DRV $EC_{50}$, and 2/10 C24h were just above this threshold (0.068 and 0.069 ug/mL). Nearly all AEs related to study drugs were mild or moderate in severity; one grade 3 direct bilirubin increase occurred and was deemed possibly related to DRV/c and INH and probably related to RPT.

**Conclusion:** DRV exposures were decreased with 3HP coadministration vs. DRV alone. Multiple trough concentrations fell below the DRV $EC_{50}$. Temporal relationships between 3HP coadministration and the extent of induction or mixed inhibition/induction of DRV metabolism were apparent. Coadministration of DRV/c with 3HP should be avoided.

**Table. PK Parameters for DRV Alone and in Combination with 3HP**

| PK Parameter | DRV/c alone (Day 4) (n=13) | DRV/c + 3HP (Day 14) (n=11) | DRV/c + 3HP (Day 19) (n=10) | Day 14 vs. Day 4 | Day 19 vs. Day 4 |
|---|---|---|---|---|---|
| $AUC_{0\text{-}24h}$ (hr*ug/mL) | 82.6 (59.9%) | 23.1 (56.8%) | 49.4 (37.6%) | 0.29 (0.24, 0.35) | 0.64 (0.53, 0.78) |
| $C_{max}$ (ug/mL) | 7.86 (42.2%) | 4.53 (45.7%) | 6.22 (39.3%) | 0.59 (0.50, 0.69) | 0.83 (0.70, 0.98) |
| $C_{0h}$ (ug/mL) | 1.75 (112%) | 0.08 (82.0%) | 0.33 (90.1%) | 0.04 (0.03, 0.07) | 0.19 (0.11, 0.34) |
| $C_{24h}$ (ug/mL) | 1.24 (122%) | 0.04 (122.0%) | 0.12 (66.2%) | 0.04 (0.02, 0.06) | 0.11 (0.07, 0.18) |
| $t_{1/2}$ (hr) | 10.8 (85.0%) | 4.44 (31.2%) | 3.37 (11.3%) | 0.45 (0.37, 0.56) | 0.35 (0.28, 0.43) |
| $CL_{ss}/F$ (L/hr) | 9.68 (59.9%) | 34.6 (56.8%) | 16.2 (37.6%) | 3.44 (2.87, 4.12) | 1.55 (1.29, 1.88) |
| V/F (L) | 151.3 (53.1%) | 221.8 (78.9%) | 78.8 (34.8%) | 1.54 (1.23, 1.93) | 0.53 (0.42, 0.67) |

Key: $AUC_{0\text{-}24h}$ = area under the concentration time curve from time 0 through 24 hours post-dose; $C_{max}$ = maximum concentration; $C_{0h}$ = time 0 (pre-dose) concentration; $C_{24h}$ = concentration at 24 hours post-dose; $t_{1/2}$ = half-life; $CL_{ss}/F$ = apparent oral clearance at steady-state; V/F = apparent volume of distribution.
Data for each phase presented as geometric mean (geometric CV%); phase comparisons presented as GMR (90% CI). All GMRs were statistically significant (p <0.05).

## 432 ISLATRAVIR DOES NOT PROLONG QTc IN A THOROUGH QT STUDY IN HEALTHY PARTICIPANTS

**Randolph P. Matthews**[1], Yang Liu[1], Catherine Matthews[1], Kristin Butterfield[1], Terry O'Reilly[2], Selwyn A. Stoch[1], Marian Iwamoto[1]
*[1]Merck & Co, Inc, Kenilworth, NJ, USA, [2]Celerion, Tempe, AZ, USA*

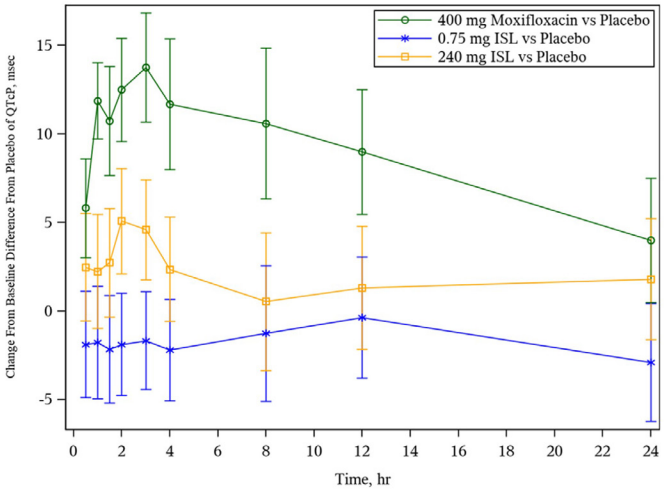
**Background:** Islatravir (ISL) is a nucleoside analog currently in development as treatment for HIV-1 and as PrEP in several dosing paradigms. Throughout clinical development, including single doses up to 400 mg, ISL has been well tolerated without related cardiac events. Preclinical work demonstrates that ISL does not interact with the hERG channel at clinically meaningful concentrations, and thus the likelihood of an effect on cardiac repolarization is low.

**Methods:** This Phase I double-blind placebo-controlled trial consisted of 4 sequences and 2 treatment periods, with a total enrollment of 63 healthy study participants. Moxifloxacin (400 mg) and placebo were tested in a crossover manner, and both a supratherapeutic dose (240 mg) and the daily therapeutic dose (0.75 mg) of islatravir were assessed after single dose oral administration. Participants were domiciled and placed on Holter monitoring to collect the pre-dose readings through 24 hours post dosing, and also had scheduled triplicate 12-lead ECG assessments. PK assessments were obtained at specified timepoints while participants were domiciled, and then concurrently with the 12-lead ECG assessments.

**Results:** Islatravir was generally well tolerated at both the 0.75 mg and 240 mg dose. As shown in Figure 1, the placebo corrected change from baseline QTcP (ΔΔQTcP) associated with both 0.75 mg and 240 mg ISL was less than 10 ms at all timepoints. In addition, exposure-response analysis showed that the ΔΔQTcP at the observed geometric mean $C_{max}$max associated with both 0.75 mg and 240 mg ISL was less than 10 ms, while 400 mg moxifloxacin (positive control) led to a ΔΔQTcP of >10 ms, as expected.

**Conclusion:** Islatravir, at the therapeutic dose of 0.75 mg and at a supratherapeutic dose of 240 mg, does not prolong QTc.

**Figure 1. QTcP Change From Baseline Difference From Placebo (LS Mean Difference With 90% CI) by Time Point and Treatment (N=28 for 0.75 mg islatravir [ISL], N=26 for 240 mg islatravir, N=28 for moxifloxacin)**




## 433 EVALUATION OF POTENTIAL DRUG-DRUG INTERACTIONS BETWEEN ISLATRAVIR AND LENACAPAVIR

**Haeyoung Zhang**[1], Eva Mortensen[1], Martin Rhee[1], Luxi Cao[1], Aaron M. Share[1], John Ling[1], Ramesh Palaparthy[1]
*[1]Gilead Sciences, Inc, Foster City, CA, USA*

**Background:** Co-administration of islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor, and lenacapavir (LEN), a capsid inhibitor, has the potential to offer a safe and efficacious oral once weekly regimen for the treatment of HIV-1 infection. ISL is not a substrate of cytochrome P450 (CYP) enzymes and is primarily metabolized via adenosine deaminase, with significant elimination via urinary excretion; ISL also has no effect on CYP enzymes or major transporters. LEN is a substrate of CYP3A, uridine diphosphate-glucuronosyl transferase 1A1, and P-glycoprotein transporter, and is a moderate inhibitor of CYP3A. Available data indicate that significant systemic drug-drug interactions (DDIs) between ISL and LEN are unlikely. This clinical study examined potential DDIs between ISL and LEN following oral co-administration.

**Methods:** A Phase I, open label, parallel design, single dose, three-cohort study was conducted in 56 healthy volunteers, who received single oral doses of co-administered ISL 20 mg and LEN 600 mg (test), ISL 20 mg alone (reference), or LEN 600 mg alone (reference). Plasma pharmacokinetic (PK) samples were collected up to Day 12 for ISL and Day 43 for LEN and analyzed with high-performance liquid chromatography tandem mass spectrometry using validated methods. DDI assessment was performed using the geometric least-squares mean (GLSM) ratios and 90% confidence intervals (CIs) of test versus reference treatments. With 15 evaluable participants per cohort, no-effect boundaries

were defined as 60%-167%, with ≥ 90% power assuming %CV of 41.4% based on ISL area under the curve (AUC) from a previous study.

**Results:** Co-administration of ISL and LEN was generally well-tolerated, with no serious or severe adverse events or clinically significant grade 3-4 lab abnormalities. Preliminary results based on nominal times for %GLSM ratios (90% CI) of PK parameters AUCinf and $C_{max}$ for ISL were 105% (90.2-123%) and 87.9% (68.7-113%), respectively, and for LEN 88.6% (60.5-130%) and 80.1% (50.9-126%), respectively. Higher %CV was observed for LEN compared to ISL, resulting in a wider 90% CI. Point estimates of %GLSM ratios and 90% CIs show that PK of ISL and LEN are similar when administered alone or in combination.

**Conclusion:** Preliminary data showed no significant DDIs for oral co-administration of ISL and LEN. Data from this study support the ongoing clinical development of co-administered ISL and LEN as a combination therapy for treatment of HIV-1 infection.

Table 1. Preliminary PK Parameter Estimates and Comparisons

| PK Parameter Mean (%CV) | ISL + LEN Co-administered (n=18) | Reference: ISL alone (n=16) or LEN alone (n=18) | ISL+LEN vs Reference %GLSM Ratio (90%CI) |
|---|---|---|---|
| **Islatravir (ISL)** | | | |
| $C_{max}$ (ng/mL) | 145 (41.3) | 165 (42.2) | 87.9 (68.7, 113) |
| $AUC_{inf}$ (h*ng/mL) | 670 (25.3) | 641 (26.1) | 105 (90.2, 123) |
| **Lenacapavir (LEN)** | | | |
| $C_{max}$ (ng/mL) | 33.7 (77.7) | 37.9 (57.0) | 80.1 (50.9, 126) |
| $AUC_{inf}$ (h*ng/mL) | 9840 (51.0) | 10800 (56.9) | 88.6 (60.5, 130) |

$AUC_{inf}$= area under the curve from zero to infinity; $C_{max}$= maximum concentration; CV= coefficient of variation; GLSM= geometric least-squares mean; CI= confidence interval
Data is shown to 3 significant digits

## 434 PHARMACOKINETICS OF LENACAPAVIR IN PARTICIPANTS WITH SEVERE RENAL IMPAIRMENT

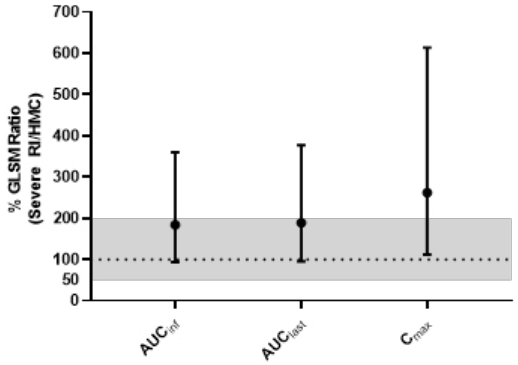
**Elijah Weber**[1], Hiba Graham[1], Steve West[1], John Ling[1], Martin Rhee[1], Ramesh Palaparthy[1]
[1]*Gilead Sciences, Inc, Foster City, CA, USA*

**Background:** Lenacapavir (LEN, GS-6207), a novel, first-in-class, selective inhibitor of HIV-1 capsid function, is in clinical development for the treatment and prevention of HIV-1 infection. Both preclinical and clinical observations suggest fecal excretion as the primary pathway, with renal excretion as a minor pathway of LEN elimination (<1% of dose). This Phase I study evaluated the pharmacokinetics (PK) of single oral dose LEN in participants with severe renal impairment (RI) to inform LEN dosing in people with impaired renal function.

**Methods:** Ten participants with stable, severe RI (creatinine clearance by Cockcroft-Gault method [CrCl] 15 to ≤ 29 mL/min) and 10 healthy matched controls (HMC) with normal renal function received a single oral dose of LEN (300 mg) on Day 1. Plasma concentrations of LEN were collected over 48 hours on Day 1 with single PK samples collected anytime on Days 4, 6, 8, 15, 22, 29, 36, 43, and 50, quantified by validated LC-MS/MS methods. Geometric least squares mean ratios (GLSMRs) and 90% confidence intervals (CIs) of AUCinf, AUClast, and $C_{max}$ were calculated to compare PK changes in participants with severe RI versus HMC. Plasma protein binding of LEN was evaluated. Safety (adverse events [AEs], clinical lab assessments, and vital signs) was monitored throughout the study.

**Results:** In participants with severe RI (median CrCl = 21.9 mL/min), exposures (AUCinf, AUClast, and $C_{max}$) of LEN were 84%, 89%, and 162% higher, respectively, relative to HMC with normal renal function (median CrCl = 98.4 mL/min) (Figure). Unbound fractions (~0.2%) of LEN were similar between severe RI and HMC groups. LEN was generally well tolerated in both groups. No participant experienced serious or Grade 4 AEs, or AEs leading to premature discontinuation of study drug. One participant in the severe RI group experienced a serious Grade 1 AE of melena, which resolved and was not considered related to study drug.

**Conclusion:** LEN was generally well-tolerated. LEN exposure was moderately higher in participants with severe RI compared to HMC. These increases, despite renal excretion being a minor pathway of LEN elimination, were potentially due to the broader effect of uremic toxins on P-gp (ie, decreased activity of P-gp-mediated LEN transport) and alterations in metabolic enzymes. Based on the totality of available LEN safety data across clinical studies, the moderate increase in LEN exposure was not deemed clinically meaningful.




Summary of GLSM ratio and 90% CIs calculated to compare the PK (AUC and Cmax) changes in participants with severe RI relative to HMC. Comparable exposures are indicated by % GLSM ratio value of 100 represented as the dotted horizontal line and the interval 50 to 200 % GLSM is represented by the shaded area.

## 435 REMOVAL OF DORAVIRINE BY HEMODIALYSIS IN HIV-INFECTED PATIENTS

**Jose Molto**[1], Fredzzia Graterol[1], Adrià Curran[2], Natalia Ramos[2], Arkaitz Imaz[3], Diego Sandoval[3], Francisco Perez[4], Lucia Bailon[1], Saye Khoo[5], Laura Else[5], Bonaventura Clotet[1]
[1]*Hospital Universitari Germans Trias i Pujol, Badalona, Spain,* [2]*Hospital Universitari Vall d'Hebron, Barcelona, Spain,* [3]*Bellvitge University Hospital, Barcelona, Spain,* [4]*Lluita contra la Sida Foundation, Badalona, Spain,* [5]*University of Liverpool, Liverpool, UK*

**Background:** Doravirine can be safely administered to HIV-infected patients with advanced kidney disease (GRF <30 ml/min). However, little is known about doravirine pharmacokinetics in patients with end-stage renal disease (ESRD) on hemodialysis. Doravirine has a relatively low molecular weight and it is only 76% bound to proteins in plasma, making possible its removal from plasma by hemodialysis. Our objective, therefore, was to evaluate the effect of hemodialysis on doravirine clearance HIV-infected patients undergoing routine hemodialysis.

**Methods:** Exploratory clinical trial including HIV-infected patients with ESRD undergoing intermittent hemodialysis. After enrolment (day 1), doravirine 100 mg once daily was added to their stable cART for five days. On day 6, blood samples were collected from each patient at the beginning and at the end of a dialysis session. Additionally, paired samples of blood entering ('in') and leaving ('out') the dialyzer and resulting dialysate were collected during the dialysis session. Doravirine concentrations in plasma and in the dialysate were determined by LC-MS/MS. The ratio of doravirine concentrations in plasma after/before the hemodialysis session and the hemodialysis extraction coefficient were calculated for each participant. Descriptive analysis shows median (range) values.

**Results:** Eight patients (6/2 male/female) were included in the study. Age and BMI were 49.5 (28 – 67) years and 23.6 (17.9 – 34.2) kg/$m_2$, respectively. Seven patients underwent 4-hour online hemodiafiltration (OL-HDF) sessions while the one remaining underwent conventional hemodialysis. Doravirine dialysis extraction coefficient was 34.3% (25.8-41.4). The ratio of doravirine concentrations in plasma after/before the hemodialysis session was 0.8 (0.6 – 1.0). At the end of the hemodialysis session (time post-dose 20.8 - 27.3 hours), doravirine concentrations in plasma were 785 (101 – 1851) ng/mL.

**Conclusion:** Despite moderate removal of doravirine by hemodialysis in this study, trough doravirine concentrations in plasma remained far above the protein-binding-adjusted $EC_{50}$ (5 ng/mL). Therefore, doravirine dosage adjustments seem to be unnecessary in HIV-infected patients with ESRD undergoing intermittent hemodialysis.

## 436 PHARMACOKINETICS OF DOLUTEGRAVIR AND BICTEGRAVIR IN OBESE PEOPLE LIVING WITH HIV

New Investigator Scholar

**Mattia Berton**[1], Sara Bettonte[1], Laurent Decosterd[2], Manuel Battegay[1], Matthias Cavassini[2], Felix Stader[3], Catia Marzolini[1]
[1]*University Hospital Basel, Basel, Switzerland,* [2]*Lausanne University Hospital, Lausanne, Switzerland,* [3]*Certara UK Limited, Sheffield, UK*

**Background:** Thanks to effective antiretroviral treatments, people living with HIV have improved health and are becoming increasingly obese at a rate similar to the general population. Furthermore, treatment with some integrase inhibitors has been associated with weight gain. Generally, obese individuals

are underrepresented in clinical trials, leading to uncertainty in the drug pharmacokinetics and consequently whether a dose adjustment is needed in this special population. This study aimed to simulate the pharmacokinetics of dolutegravir and bictegravir in obese using physiologically based pharmacokinetic (PBPK) modelling verified with clinical data from the Swiss HIV Cohort Study (SHCS).

**Methods:** Obesity related physiological changes were collected from published studies, analysed, and implemented in our whole-body PBPK model, built in Matlab® R2020a. The predictive performance of the model to simulate the pharmacokinetics of CYP3A4 and UGT1A1 substrates in non-obese (BMI 18.5-30 kg/m$^2$) and obese (BMI 30-40 kg/m$^2$) was verified using published clinical data for midazolam (10mg single oral dose) and triazolam (0.25mg IV bolus in non-obese and 0.5mg IV infusion in obese), as well as SHCS data in obese for dolutegravir (50mg QD oral at steady state). The verified PBPK model was used to simulate the pharmacokinetics of the CYP3A4/UGT1A1 substrate bictegravir (50mg QD oral at steady state).

**Results:** The model was able to predict the pharmacokinetics within 1.25-fold of clinically observed data. The simulated vs observed AUC0-∞ were 189.8 vs 166.0 ng*h/mL for midazolam and 34.2 vs 30.8 ng*h/mL for triazolam in non-obese individuals. The predicted vs observed AUC0-∞ were 155.0 vs 141.2 ng*h/mL for midazolam and 50.1 vs 45.0 ng*h/mL for triazolam in obese individuals. The pharmacokinetic parameters of dolutegravir and bictegravir in non-obese and obese are summarized in Table 1. Obesity is predicted to reduce dolutegravir $C_{max}$ and AUC by 13% and 3%, respectively and bictegravir $C_{max}$ and AUC by 15% and 11%, respectively.

**Conclusion:** PBPK modelling is a useful tool to overcome limited clinical data. Our predictions verified with clinical data indicate that obesity has a modest effect on the pharmacokinetics of dolutegravir and bictegravir which does not warrant a dosage adjustment in this special population.

Table 1: Observed vs predicted pharmacokinetic parameters for dolutegravir and bictegravir in non-obese and obese individuals.

| | | Non-obese (BMI 18.5-30 kg/m²) | | Obese (BMI 30-40 kg/m²) | | Ratio obese/non-obese | |
|---|---|---|---|---|---|---|---|
| | | Observed | Predicted | Observed | Predicted | Observed | Predicted |
| Dolutegravir | $C_{max}$ (ng/mL) | 3316.9 | 3190.0 | 2884.3 | 2771.8 | 0.87 | 0.87 |
| | $AUC_{0-24}$ (ng*h/mL) | 45445.8 | 45353.5 | 43415.0 | 43876.7 | 0.96 | 0.97 |
| | $t_{1/2}$ (h) | 12.6 | 11.8 | - | 16.3 | - | 1.39 |
| Bictegravir | $C_{max}$ (ng/mL) | 5525.5 | 4095.6 | - | 3485.7 | - | 0.85 |
| | $AUC_{0-24}$ (ng*h/mL) | 80394.0 | 72689.5 | - | 64343.5 | - | 0.89 |
| | $t_{1/2}$ (h) | 20.6 | 23.4 | - | 30.7 | - | 1.31 |

## 437 STUDY 31/A5349 POPULATION PHARMACOKINETIC ANALYSIS OF RIFAPENTINE AND MOXIFLOXACIN

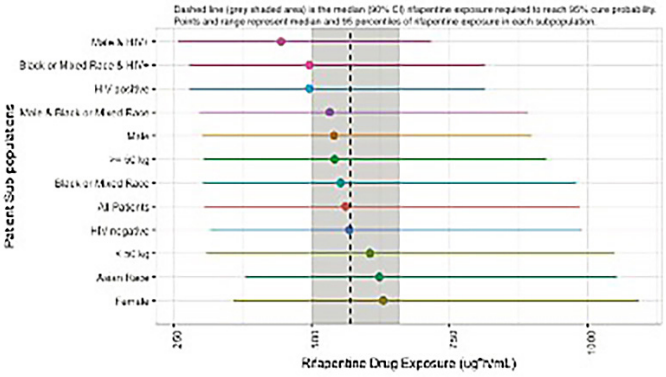
**Vincent Chang**[1], Marc Weiner[2], Marjorie Z. Imperial[1], Nan Zhang[1], William Whitworth[3], Kia Byrant[3], Melissa Engle[2], Susan Dorman[4], Payam Nahid[1], Susan Swindells[5], Richard E. Chaisson[4], Pheona Nsubuga[6], Kelly Dooley[4], Rada Savic[1]
*[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Texas at San Antonio, San Antonio, TX, USA, [3]Centers for Disease Control and Prevention, Atlanta, GA, USA, [4]The Johns Hopkins University, Baltimore, MD, USA, [5]University of Nebraska Medical Center, Omaha, NE, USA, [6]Uganda - Case Western Reserve University Research Collaboration, Kampala, Uganda*

**Background:** Study 31/A5349 (NCT02410772) was a Phase III randomized controlled trial that demonstrated noninferiority of a 4-month isoniazid, rifapentine (RPT), and pyrazinamide plus moxifloxacin (MXF) regimen compared to the 6-month standard treatment for drug-sensitive tuberculosis (TB). RPT is well known for its variability in drug exposures and is also an enzyme inducer, inducing not only its own clearance but also of MXF. Study 31 PKPD analysis demonstrated the importance of MXF for treatment success and has also identified suboptimal RPT exposure as a risk factor for TB-related unfavorable outcome. Our goal was to characterize relevant covariates and subpopulations at risk for RPT and MXF underexposure.

**Methods:** Pharmacokinetic data were available for 1523 patients for RPT and 767 patients for MXF. Patients were dosed daily with 1200 mg RPT and 400 mg MXF; samples were taken between the 2nd and 8th week, after enzyme induction reached steady state. Data were analyzed using nonlinear mixed-effects modeling.

**Results:** RPT PK was significantly modulated by race, sex, and HIV status. Overall, males, Black or mixed race people, or people living with HIV were all at risk of low RPT exposure, with male HIV+ patients at highest risk (see figure). Although body weight increased clearance, clearance only changed by 2.6% for every 10 kg increase in body weight, a clinically irrelevant effect size that explained little of the variability in clearance. We found evidence that MXF PK was lower in men and in patients with comorbidities (HIV and diabetes). The apparent clearance of MXF co-administered with 1200 mg RPT was estimated to be 16.7 L/h, which is ~40% higher compared to historically reported MXF clearance without RPT (~12 L/h). The faster clearance is likely due to RPT enzyme induction. Male, diabetic, or HIV+ patients' median MXF exposures were 20%, 24%, and 28% lower than female, non-diabetic, and HIV- patients respectively. Patients with multiple risk factors were at highest risk (such as male diabetic patients)

**Conclusion:** Higher doses for male, HIV-positive, Black or Mixed race, or people with diabetes would prevent underexposure in these at-risk subpopulations and might improve treatment outcomes. These factors are consistent with historical risk factors for poor TB treatment outcomes (male, HIV+, and Black race), suggesting that the increased risk for unfavorable outcome is due in part to low PK. RPT exposure in patients taking antiretrovirals other than efavirenz may differ from what we observed.




## 438 PHARMACOGENETICS OF BEDAQUILINE AND CLOFAZIMINE PLASMA CLEARANCE AMONG SOUTH AFRICANS

**David W. Haas**[1], Mahmoud T. Abdelwahab[2], Stijn W. van Beek[3], Paxton Baker[4], Gary Maartens[2], Yuki Bradford[5], Marylyn D. Ritchie[5], Sean Wasserman[2], Graeme Meintjes[2], Neel R. Gandhi[6], Elin Svensson[3], Paolo Denti[2], James C. Brust[7]
*[1]Vanderbilt University, Nashville, TN, USA, [2]University of Cape Town, Cape Town, South Africa, [3]Radboud University Medical Center, Nijmegen, Netherlands, [4]Vanderbilt University Medical Center, Nashville, TN, USA, [5]University of Pennsylvania, Philadelphia, PA, USA, [6]Emory University, Atlanta, GA, USA, [7]Albert Einstein College of Medicine, Bronx, NY, USA*

**Background:** Bedaquiline (BDQ) and clofazimine (CFZ) are widely used to treat drug-resistant tuberculosis (TB). BDQ is primarily metabolized by hepatic cytochrome P450 (CYP) 3A4 into the M2 metabolite. Plasma clearance of BDQ is reported to be more rapid with African ancestry. We examined whether human genetic polymorphisms explained between-individual variability in plasma clearance of BDQ, M2, and CFZ in a prospective cohort of patients treated for drug-resistant TB in South Africa.

**Methods:** Data and specimens were from the Pharmacokinetics, Resistance, and Outcomes of Bedaquiline in MDR- and XDR-TB (PROBeX) study. Genotyping with Illumina MEGAEX was followed by genome-wide imputation using the TOPMed reference panel. Drug concentration data were interpreted using previously developed non-linear mixed-effects models which included effects of age, weight, albumin, and concomitant lopinavir/ritonavir on BDQ, and effect of body composition on CFZ. Associations between pharmacogenetic polymorphisms, genome-wide polymorphisms, and variability in clearance were examined using linear regression models adjusted for the first two genetic principal components.

**Results:** 140 of 195 cohort participants were evaluable for genetic associations. Among 21 polymorphisms selected based on prior genome-wide significant associations with any drug, the CYP3A5 rs776746 loss-of-function C allele (CYP3A5*3) was associated with slower clearance of BDQ ($p = 0.0017$, which withstood correction for multiple testing) but not M2 ($p = 0.25$). CYP3A5*3

heterozygosity and homozygosity were associated with 15% (95% CI 3.5% to 25.5%) and 30% (95% CI 7.0% to 51%) slower BDQ clearance, respectively. The minor allele frequency of rs776746 was 17%. The lowest P-value for CFZ clearance was VKORC1 rs9923231 (p = 0.13). In genome-wide analyses, the lowest P-values for clearance of BDQ and CFZ were RFX4 rs76345012 (p = 6.4x10-7) and CNTN5 rs75285763 (p = 2.9x10-8), respectively.

**Conclusion:** Among South Africans treated for drug-resistant TB, CYP3A5*3 was associated with slower plasma BDQ clearance. Different CYP3A5*3 minor allele frequencies among populations (30% in Africans, 70% in East Asians, 93% in Europeans) may explain the more rapid BDQ clearance previously reported in people of African ancestry. The genome-wide significant association of CNTN5 rs75285763 with CFZ clearance is likely a chance finding.

## 439 PHARMACOGENETICS OF DOLUTEGRAVIR PLASMA EXPOSURE AMONG SOUTH AFRICANS LIVING WITH HIV

New Investigator Scholar

**Zinhle Cindi**[1], Aida N. Kawuma[1], Gary Maartens[1], Roeland E. Wasmann[1], Paolo Denti[1], Lubbe Wiesner[1], Yuki Bradford[2], Francois Venter[3], Simiso M. Sokhela[3], Nomathemba Chandiwana[3], Marylin D. Ritchie[2], David W. Haas[4], Phumla Sinxadi[1]

*[1]University of Cape Town, Cape Town, South Africa, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]University of the Witwatersrand, Johannesburg, South Africa, [4]Vanderbilt University, Nashville, TN, USA*

**Background:** Dolutegravir (DTG) is a component of preferred first-line antiretroviral therapy (ART) regimens. DTG is metabolized primarily by UGT1A1, and UGT1A1 variants affect DTG plasma exposure. There are limited data on DTG pharmacogenetics in Africa. We characterized genetic associations with estimated plasma DTG area under the concentration-time curve (AUC) among African participants who initiated DTG-containing ART in a clinical trial.

**Methods:** We studied participants who were randomized to initiate DTG in the ADVANCE study (with TAF or TDF, each with emtricitabine). A population pharmacokinetic (PK) model estimated DTG exposure, based on intensive and sparse plasma sampling at steady state. After adjusting for the expected effect of body weight with allometry, the model produced individual estimates of unexplained variability in exposure (AUCVAR). Genotyping with Illumina MEGAEX was followed by genome-wide imputation using the TOPMed reference panel. Genetic associations with AUCVAR were assessed with multivariable linear regression models adjusted for the first two genetic principal components. Primary analyses focused on variants previously reported to be associated with DTG PK, and all variants (±50 kB) in the UGT1A locus. We also explored associations genome-wide. Baseline plasma bilirubin was used as a positive control for UGT1A associations.

**Results:** 284 of 340 ADVANCE participants who consented for genetic testing were evaluable for analysis. All were Black Africans and 62% were females. Among variants of primary interest, the lowest P-value for AUCVAR was UGT1A rs887829 (P=1.8x10-4), which was also associated with $\log_{10}$ bilirubin (P=8.6x10-13). After adjusting for rs887829, bilirubin was independently associated with rs28899168 in the UGT1A locus (P=7.7x10-8). Compared to rs887829 C/C, individuals with rs887829 C/T and T/T had 6% and 28% decreases in DTG clearance, respectively, and thus greater DTG exposure. DTG AUCVAR was also independently associated with rs28899168 (P = 0.02). The lowest genome-wide P-value for DTG AUCVAR was CAMKMT rs343942 (P=2.4x10-7).

**Conclusion:** Among African participants in a prospective clinical trial, UGT1A rs887829 and rs28899168 were independently associated with DTG exposure. The novel rs28899168 association warrants independent replication.

## 440 ANTI-INFECTIVES' PENETRATION IN UPPER AND LOWER FEMALE GENITAL TISSUES

New Investigator Scholar

**Fan Wang**[1], Olivie C. Namuju[2], Katelyn A. Pastick[1], Kizito Abdusalaamu[2], Usha Mishra[1], Lindsey B. Collins[1], David R. Boulware[1], Robert Lukande[3], David Meya[3], Melanie R. Nicol[1]

*[1]University of Minnesota, Minneapolis, MN, USA, [2]Infectious Disease Institute, Kampala, Uganda, [3]Makerere University, Kampala, Uganda*

**Background:** Understanding drug exposure in the female genital tract (FGT) is paramount in the treatment and prevention of infectious diseases. We sought to explore tissue penetration of three anti-infective agents-- tenofovir (TFV), lamivudine (3TC), and fluconazole, in FGT tissues (i.e., ovary, uterus, cervix, and vagina) from women living with HIV. While drug exposure in lower FGT tissues (eg, cervix, vagina) has been well described, little data exist on upper genital tissues (eg, ovary, uterus).

**Methods:** With next-of-kin consent, autopsies were performed within 24h of death for female participants with advanced HIV in Uganda (n=27). Approximately 78% of participants were receiving tenofovir disoproxil fumarate (TDF, prodrug of TFV) or 3TC at time of death, while 44% were receiving fluconazole. Postmortem tissue samples were snap frozen and stored at -80°C until analysis. We measured TFV, 3TC, and fluconazole concentrations using high-performance liquid chromatography-tandem mass spectrometry in plasma as well as ovarian, uterine, cervical, and vaginal tissues. We calculated tissue penetration as tissue-to-plasma ratios (TPRs), assuming a tissue density of 1g/mL.

**Results:** Median concentration of TFV was highest in vaginal (4647 ng/mL) and lowest in uterine tissue (2357 ng/mL); for 3TC, highest was vaginal (8265 ng/mL) and lowest was uterine tissue (3912 ng/mL); for fluconazole, highest was ovarian (30.8 µg/mL) and lowest was cervical tissue (22.6 µg/mL). TPRs are shown in Figure. When comparing TPRs to cervical tissue, we found vaginal TPRs significantly higher than cervical for TFV (p=0.02), 3TC (p=0.005) and fluconazole (p=0.02). Overall, the proportions of individuals with TPRs greater than 1 in FGT were similar for TFV and 3TC (70% and 71%, respectively), but lower for fluconazole (23%). For all 3 drugs, the proportion of TPR ≥1 was highest in vagina. Time between death and autopsy was not significantly associated with the TPR for TFV (p=0.6), 3TC (p=0.8) nor fluconazole (p=0.3) by linear mixed effect model, suggesting no significant repartition during the postmortem interval.

**Conclusion:** This is the first study to explore FGT penetration of 3 anti-infectives in a Ugandan population with advanced HIV. Significant differences between cervical and other female genital compartments were identified. Approximately 70% of the participants had a TPR greater than 1 for TFV and 3TC, suggesting adequate penetration for prevention of HIV transmission.

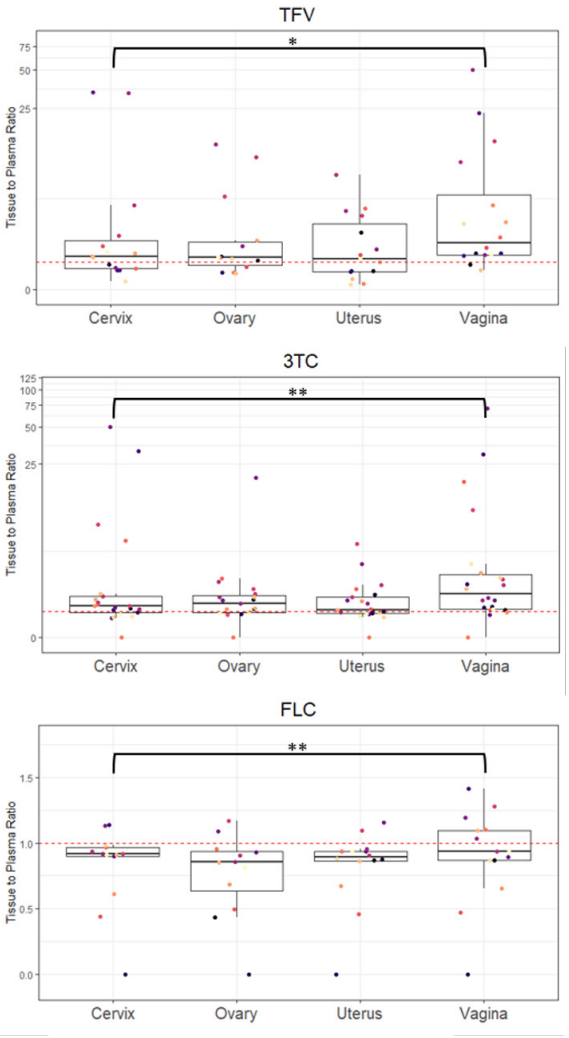



**Figure.** Tissue-to-plasma ratios (TPRs) of TFV (A), 3TC (B) and fluconazole (FLC) (C) for cervix, ovary, uterus and vagina. In each plot, points with the same color representing a same individual. TPRs in vagina are significantly higher than in cervix for TFV, 3TC and FLC (p-values = 0.02, 0.005 and 0.02, paired Wilcoxon test). The red dashed line represents TPR=1. TPRs in (A) and (B) are demonstrated on log scale.

## 441 ORAL TDF/FTC PROVIDES EARLY MUCOSAL PROTECTION IN BOTH ON-DEMAND AND DAILY REGIMEN

**Sylvain Chawki**[1], Audrey Gabassi[1], Mayssam El Mouhebb[2], Milad Taouk[1], Lambert Assoumou[2], Iris Bichard[1], Skander Benothmane[1], Ali Amara[3], Rhonda Brand[4], Aaron Siegel[4], Lauriance Goldwirt[1], Ian McGowan[5], Dominique Costagliola[2], Jean-Michel Molina[1], Constance Delaugerre[1]

*[1]Hôpital Saint-Louis, Paris, France, [2]Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France, [3]Institut National de la Santé et de la Recherche Médicale, Paris, France, [4]University of Pittsburgh, Pittsburgh, PA, USA, [5]Orion Biotechnology, Ottawa, Canada*

**Background:** Oral pre-exposure prophylaxis (PrEP) with TDF/FTC is efficacious in preventing HIV acquisition in MSM, both with ON-DEMAND and the DAILY regimens. Whether a PrEP effect occurs at the mucosal level after the recommended pre-exposure dose remains uncertain. We aimed to study TDF/FTC PrEP mucosal efficacy against HIV in an ex vivo rectal tissue model with either PrEP dosing regimen.

**Methods:** We designed a substudy of the ANRS-PREVENIR study (NCT 03113123) of participants taking either ON-DEMAND or DAILY PrEP. We used an ex vivo infection challenge model to evaluate rectal tissue susceptibility to HIV infection before and after PrEP exposure, where each participant was his own control, thus estimating the level of protection provided by TDF/FTC. Rectal explants were collected at baseline and 2 hours after a double dose of TDF/FTC or 7 days after one pill a day in the ON-DEMAND and DAILY arms, respectively. HIV infectability was evaluated by measuring rectal explant supernatant p24 secretion over 14 days of culture. Levels of p24 were standardized by the weight of each explant (ng/ml/mg of tissue). Mean D14 cumulative p24 level differences (After-Before PrEP) reflect overall infectability of explants in each patient. Comparison between before and after PrEP was done using a paired-Wilcoxon test. Comparison between PrEP dosing regimens was done using a Mann-Whitney test.

**Results:** We included 13 individuals in the ON-DEMAND group and 12 in the DAILY group. All participants were self-identifying MSM and gave written consent. We excluded 2 individuals (one in each group) for insufficient infection of rectal tissue before PrEP. The median of mean D14 cumulative p24 difference after-before PrEP was -144ng/ml/mg (IQR[-259;-108]) for the ON-DEMAND group (P=.0005, n=12) (Figure). The median of mean D14 cumulative p24 difference after-before PrEP was -179ng/ml/mg (IQR[-253;-86]) for the DAILY group (P=.001, n=11) (Figure). There was no statistical difference in the median cumulative p24 differences between the groups, for a sample of 23 participants analyzed (P=0.93).

**Conclusion:** ON-DEMAND and DAILY PrEP with TDF/FTC both showed efficacy to reduce HIV infection, as soon as 2 hours for the ON-DEMAND arm, in rectal tissue. PrEP efficacy in rectal tissue might be a good marker of clinical efficacy that needs to be evaluated for future PrEP agents or dosing strategy candidates.

**Table. PK Parameters for DRV Alone and in Combination with 3HP**

| PK Parameter | DRV/c alone (Day 4) (n=13) | DRV/c + 3HP (Day 14) (n=11) | DRV/c + 3HP (Day 19) (n=10) | Day 14 vs. Day 4 | Day 19 vs. Day 4 |
|---|---|---|---|---|---|
| $AUC_{0\text{-}24h}$ (hr*ug/mL) | 82.6 (59.9%) | 23.1 (56.8%) | 49.4 (37.6%) | 0.29 (0.24, 0.35) | 0.64 (0.53, 0.78) |
| $C_{max}$ (ug/mL) | 7.86 (42.2%) | 4.53 (45.7%) | 6.22 (39.3%) | 0.59 (0.50, 0.69) | 0.83 (0.70, 0.98) |
| $C_{0h}$ (ug/mL) | 1.75 (112%) | 0.08 (82.0%) | 0.33 (90.1%) | 0.04 (0.03, 0.07) | 0.19 (0.11, 0.34) |
| $C_{24h}$ (ug/mL) | 1.24 (122%) | 0.04 (122.0%) | 0.12 (66.2%) | 0.04 (0.02, 0.06) | 0.11 (0.07, 0.18) |
| $t_{1/2}$ (hr) | 10.8 (85.0%) | 4.44 (31.2%) | 3.37 (11.3%) | 0.45 (0.37, 0.56) | 0.35 (0.28, 0.43) |
| $CL_{ss}/F$ (L/hr) | 9.68 (59.9%) | 34.6 (56.8%) | 16.2 (37.6%) | 3.44 (2.87, 4.12) | 1.55 (1.29, 1.88) |
| V/F (L) | 151.3 (53.1%) | 221.8 (78.9%) | 78.8 (34.8%) | 1.54 (1.23, 1.93) | 0.53 (0.42, 0.67) |

Key: $AUC_{0\text{-}24h}$ = area under the concentration time curve from time 0 through 24 hours post-dose; $C_{max}$ = maximum concentration; $C_{0h}$ = time 0 (pre-dose) concentration; $C_{24h}$ = concentration at 24 hours post-dose; $t_{1/2}$ = half-life; $CL_{ss}/F$ = apparent oral clearance at steady-state; V/F = apparent volume of distribution.
Data for each phase presented as geometric mean (geometric CV%); phase comparisons presented as GMR (90% CI). All GMRs were statistically significant (p <0.05).

## 442 PK/PD RESULTS OF CHAPS ORAL PREEXPOSURE PROPHYLAXIS TRIAL IN FORESKIN TISSUE

New Investigator Scholar

**Carolina Herrera**[1], Laura Else[2], Emily Webb[3], Azure-Dee A. Pillay[4], Thabiso B. Seiphetlo[4], Limakatso Lebina[5], Jennifer Serwanga[6], Christian Callebaut[7], Robin Shattock[1], Francesca Chiodi[8], Clive Gray[4], Saye Khoo[2], Neil A. Martinson[5], Julie Fox[9]

*[1]Imperial College London, London, UK, [2]University of Liverpool, Liverpool, UK, [3]London School of Hygiene & Tropical Medicine, London, UK, [4]University of Cape Town, Cape Town, South Africa, [5]Perinatal HIV Research Unit, Soweto, South Africa, [6]Uganda Virus Research Institute, Entebbe, Uganda, [7]Gilead Sciences, Inc, Foster City, CA, USA, [8]Karolinska Institute, Stockholm, Sweden, [9]King's College London, London, UK*

**Background:** On demand pre-exposure prophylaxis (PrEP) in msm has not been evaluated in Africa and the dosing requirement for insertive sex is unknown. The CHAPS trial (NCT03986970) aims to optimize on-demand PrEP dosing for insertive sex for young men in sub-Saharan Africa.

**Methods:** Phase II open-label, randomised controlled trial (RCT) in Uganda and South Africa of 144 HIV negative men aged 13-24yrs, eligible for voluntary medical male circumcision (VMMC) and randomized to one of 9 arms receiving F/TDF, F/TAF or no PrEP at 1 (2 tablets) or 2 (2+1 tablets) consecutive days with final dose 5 or 21h prior to VMMC. Inner and outer foreskins explants were exposed to HIV-1BaL at a high (HVT) or a more biological relevant, low viral titre (LVT). Explants were further dosed ex vivo using the same oral PrEP drug 20h post-challenge. Infection was assessed at different time points during 15 days of culture by measurement of p24 in culture supernatants. TFV-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) tissue levels were measured using LC-MS methods (LLQ = 0.04 pmol/sample). Parallel systemic PK/PD evaluation was performed in isolated PBMCs at VMMC. We present data from South Africa.

**Results:** Tissue TFV-DP concentrations (detected in 88% of tissue samples) were ~2-fold higher with F/TAF vs. F/TDF dosing (p=0.02). FTC-TP levels were ~10-fold higher than TFV-DP, and no significant differences were seen between regimens. TFV-DP levels were ~40% higher with 2+1 vs. 2 tablets F/TDF dosing. No TFV-DP dose accumulation was evident for F/TAF. Following ex vivo HIV-1BaL challenge, greater decrease of p24 relative to control arm was observed with 2+1 than with 2 PrEP tablets dosing (F/TDF dosing: p=0.24 for HVT; 0.62 LVT; F/TAF dosing: p=0.12 for HVT; 0.39 LVT). Further decrease was observed in PBMCs (F/TDF dosing: p=0.20 for HVT; 0.57 LVT; F/TAF dosing: p=0.07 for HVT; 0.57 LVT). Ex vivo protection levels against LVT with F/TDF and F/TAF were not significantly different.

**Conclusion:** Oral on demand PrEP dosing with 2 tablets of F/TDF or F/TAF from 5-21h before HIV-exposure provides ex vivo protection of foreskin tissue which increases with 2+1 dosing. PrEP efficacy needs to be evaluated in blood and mucosal compartments. Ex vivo challenge studies in human foreskin explants may facilitate dosing requirements and evaluation of new drugs for PrEP.

| | | [Metabolites] (pmol/g) GM (95% CI) | | [p24]$_{day\ 15}$ (pg/ml) GM (95% CI) | | | |
|---|---|---|---|---|---|---|---|
| | | Tissue | | Tissue | | PBMCs | |
| PrEP | Dosing | TFV-DP | FTC-TP | HVT | LVT | HVT | LVT |
| F/TDF | 2 tablets | 11.91 (7.10-19.96) | 254.5 (149.2-434.4) | 29.94 (19.21-46.67) | 5.399 (3.157-9.232) | 1262 (661.9-2407) | 36.16 (16.55-79) |
| | 2+1 tablets | 16.56 (9.97-27.53) | 236.3 (139.3-400.8) | 20.81 (13.11-33.03) | 4.53 (2.718-7.549) | 685 (310.1-1513) | 27.17 (13.46-54.85) |
| F/TAF | 2 tablets | 28.67 (17.55-46.83) | 234.5 (140.6-391.0) | 42.48 (24.91-72.44) | 5.953 (2.779-12.75) | 447.4 (212.7-941.3) | 37.24 (17.81-77.9) |
| | 2+1 tablets | 23.71 (12.06-46.64) | 116.3 (43.73-309.1) | 25.89 (17.46-38.41) | 5.363 (3.373-8.527) | 946.7 (512.8-1748) | 32.11 (19.09-54) |
| Control | 0 tablets | N/D | N/D | 441.4 (320.8-607.3) | 53.24 (24.14-117.4) | 9317 (8282-10480) | 1460 (474.8-4491) |

GM: geometric mean; CI: confidence interval; N/D: not detected

## 443 ANAL SEX & TENOFOVIR DOUCHE SEQUENCE IMPACT COLORECTAL DISTRIBUTION OF HIV & DOUCHE

**Lynn N. Bertagnolli**[1], Sandra Abdul Massih[2], Craig W. Hendrix[1], Sridhar Nimmagadda[1], Edward J. Fuchs[1]

*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins University, Baltimore, MD, USA*

**Background:** Men who have sex with men (MSM) are at high risk of HIV acquisition through unprotected receptive anal intercourse (URAI). This group accounts for the majority of the U.S. epidemic, as 69% of new HIV infections occur in MSM; however, URAI is also a significant HIV risk for trans- and cisgender women. Oral tenofovir (TFV)/emtricitabine (FTC), vaginal dapivirine ring, and injectable cabotegravir proved effective as HIV PrEP. However, vaginal rings do not protect from rectal HIV exposures, some persons at risk of HIV

find adherence to oral PrEP challenging, some prefer avoidance of systemic drug exposure, and some prefer behaviorally-congruent PrEP options (adding antiretroviral drugs to products commonly used with sex, eg, lubes and douches). We developed an on demand, behaviorally-congruent rectal TFV douche as a PrEP option for URAI. The TFV douche provided superior protection for rectal SHIV challenge in macaques vs. oral TFV/FTC and exceeded colon tissue active TFV concentration vs. the on demand Ipergay 2+1+1 TFV/FTC regimen in clinical studies.

**Methods:** Our goal was to compare colorectal distribution of an HIV surrogate & TFV douche when the TFV douche preceded or followed simulated receptive anal intercourse (sRAI). Five participants were enrolled for two study visits. At the first study visit, participants received an 111In-labeled TFV douche prior to sRAI using 99mTc-sulfur colloid in autologous semen as HIV surrogate. At the second study visit, the radiolabeled TFV douche was administered following radiolabeled sRAI. The primary outcome measure was the colorectal distribution of both douche and HIV radioisotopes using SPEC/CT.

**Results:** The colorectal distribution of the TFV douche was equal to or greater than the HIV surrogate in all participants, regardless of the sequence, with one exception (J204 sRAI before douche), where the HIV surrogate had greater distribution toward the anus (Table). In all participants, the gastrointestinal distribution of the HIV surrogate increased when the douche was administered following sRAI.

**Conclusion:** Colorectal distribution of a TFV douche matched or exceeded the HIV surrogate in all participants, providing similar anatomic coverage as the HIV surrogate. The colorectal distribution of the HIV surrogate was greater when the TFV douche was administered following sRAI, therefore, douching following RAI may increase HIV distribution in the colon with uncertain, potentially increased, risk for HIV acquisition.

**Table.** Colorectal distribution of TFV douche ($^{111}$In-DTPA) preceding and following simulated receptive anal intercourse (sRAI) with HIV surrogate ($^{99m}$Tc-Sulfur colloid) by sequence of douche and sRAI.

| PID | Sequence | $^{111}$In TFV Douche | $^{99m}$Tc "HIV" Surrogate | Distribution |
|---|---|---|---|---|
| J202 | TFV douche -> sRAI | R to S | R | TFV > "HIV" |
| J202 | sRAI -> TFV douche | R to DC | R to DC | TFV = "HIV"; increased distribution v. douche -> sRAI |
| J203 | TFV douche -> sRAI | R to S | R to S | TFV = "HIV" |
| J203 | sRAI -> TFV douche | R to DC | R to DC | TFV = "HIV"; increased distribution v. douche -> sRAI |
| J204 | TFV douche -> sRAI | R to DC | R | TFV > "HIV" |
| J204 | sRAI -> TFV douche | S to DC | R to DC | "HIV" > TFV; increased distal distribution v. douche -> sRAI |
| J205 | TFV douche -> sRAI | R to DC | R | TFV > "HIV" |
| J205 | sRAI -> TFV douche | R to SF | R to SF | TFV = "HIV"; increased distribution v. douche -> sRAI |
| J206 | TFV douche -> sRAI | R | R | TFV = "HIV" |
| J206 | sRAI -> TFV douche | R to S | R to S | TFV = "HIV"; increased distribution v. douche -> sRAI |

R: Rectum; S: Sigmoid colon; DC: Descending Colon; SF: Splenic Flexure

## 444 PHARMACOKINETIC STUDY OF ISLATRAVIR & ETONOGESTREL IMPLANTS IN MACAQUES

**Michele B. Daly**[1], Andres Wong-Sam[1], Linying Li[2], Archana Krovi[2], Gregory Gatto[2], Victoria Mrotz[1], Catalina Forero[1], Joy Gary[1], James Mitchell[1], Ariane Van der Straten[3], Walid Heneine[1], Gerardo Garcia-Lerma[1], Charles Dobard[1], Leah Johnson[2]

*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]RTI International, Research Triangle Park, NC, USA, [3]University of California San Francisco, San Francisco, CA, USA*

**Background:** Prevention of HIV and unintended pregnancies are public health priorities. We assessed the pharmacokinetics of ε-polycaprolactone implants containing the antiretroviral islatravir (ISL) and the contraceptive etonogestrel (ENG) in macaques.

**Methods:** ISL implants (100µm wall thickness) were administered subcutaneously in the right arm with a trocar. Group-1 (n=3) received a low-dose (LD) and group-2 (n=3) received a mid-dose (MD) ISL implant with an in vitro release-rate (IRR) of 42 and 75 µg/day, respectively. After 4 weeks, group-1 received a second ISL implant with an IRR of 75 µg/day in the left arm to assess a high-dose (HD) of ISL with a cumulative IRR of 117 µg/day. Group-2 received an ENG implant (300µm wall thickness) with an IRR of 40 µg/day in the left arm to assess co-release of ISL and ENG. Blood collections and visual exams were done weekly, and mucosal biopsies were collected biweekly for 14 weeks. ISL, ENG, and progesterone (P4) were measured in plasma and ISL triphosphate (ISL-TP) was measured in PBMCs and tissues. Implant site reactions were scored with a modified Draize scale (0-4) and skin biopsies collected near the implant were H&E stained. PK data from broken implants was excluded from analysis.

**Results:** Plasma ISL levels were 0.38, 0.60, and 0.88 ng/ml for the LD, MD±ENG, and HD groups, respectively. ISL-TP in PBMCs were sustained for >3 months [LD=24.8, MD±ENG =41.8, HD=75.8 fmol/10^6 cells], but only the HD group achieved levels above the PrEP benchmark (50 fmol/10^6 cells). ISL-TP was detected in vaginal tissue [median: LD=12.2, MD±ENG=14.6, HD=31.3] and rectal tissue [median: LD=18.5, MD±ENG=20.8, HD=30.2 fmol/mg tissue]. P4 production was suppressed by week 2 and plasma ENG peaked at week 3 [875 pg/ml]. No local reactions were observed at implant sites with intact ISL (n=7/9) and ENG (n=3/3) implants. H&E-stained skin biopsies were pathologically unremarkable. Two MD ISL implants broke on day 49 and 56 post-implantation, but only mild redness and edema were observed [median Draize score = 1 (range 0.5-2)].

**Conclusion:** Implants yielded stable plasma ISL and ISL-TP in PBMCs for >3 months with minimal implant-site reactions when intact. Based on the initial ISL load and estimated IRR, the sustained release of ISL is projected for >2 years. Plasma ENG levels were stable and sufficient to fully suppress progesterone. Evaluation of optimized implants with increased wall thickness is underway for improved durability and vaginal efficacy in a SHIV challenge model.

| Islatravir Implants | Drug (In vitro release rate) | Location and duration | | Median [range] | |
|---|---|---|---|---|---|
| | | Right Arm (weeks implanted) | Left Arm (weeks implanted) | Plasma ISL (ng/ml) | PBMC ISL-TP (fmol/10^6 cells) |
| Low Dose | ISL (42 ug/day) | LD (w1-4) | n/a | 0.39 [0.36-0.54] | 26.7 [21.8-32.6] |
| Mid Dose ± ENG | ISL (75 ug/day) ENG (40 ug/day) | MD (w1-13) | ENG (w5-19) | 0.59 [0.49-0.75] | 42.5 [20.1-96.5] |
| High Dose | ISL (117 ug/day) | LD (w1-19) | MD (w5-19) | 0.88 [0.66- 3.4] | 79.5 [46.5-229.0] |

## 445 NEXT-GENERATION ISLATRAVIR/ETONOGESTREL/ETHINYL ESTRADIOL MPT INTRAVAGINAL RING

**Isabella Young**[1], Roopali Shrivastava[1], Rima Januszewicz[1], Craig Sykes[1], Mackenzie L. Cottrell[1], Cynthia Cabrales[2], Angela Kashuba[1], David Katz[3], Richard Pyles[2], Kathleen L. Vincent[2], Rahima Benhabbour[1]

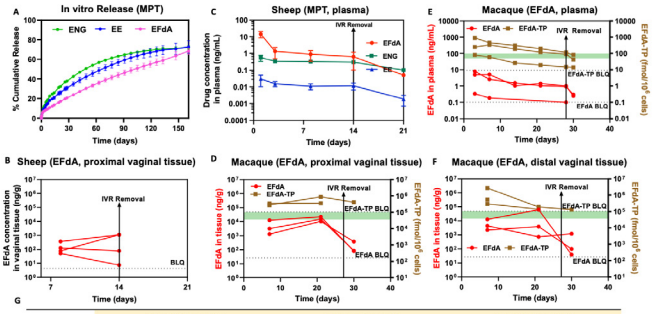
*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]University of Texas at Galveston, Galveston, TX, USA, [3]Duke University, Durham, NC, USA*

**Background:** Multipurpose prevention technologies (MPTs) are of interest to prevent unintended pregnancy and HIV. Uniquely designed, geometrically complex 3D printed intravaginal rings (IVRs) are an attractive delivery platform that can provide controlled drug release and tunable product user characteristics. We evaluated drug release, elimination, and safety of an MPT IVR in sheep and an Islatravir (EFdA)-eluting, HIV PrEP IVR in NHP.

**Methods:** IVRs were manufactured using Continuous Liquid Interface Production (CLIP™) 3D printing and EFdA, ethinyl estradiol (EE), and etonogestrel (ENG) were formulated individually or in combination. MPT IVRs (4.03-6.48 mg/kg EFdA, 0.05-0.07 mg/kg EE and 0.2-0.3 mg/kg ENG) were administered to 4 female sheep; and EFdA, EE and ENG were quantified in plasma and vaginal tissues and fluids over 14 days of insertion then 7 days after removal. Safety was assessed by colposcopy, optical coherence tomography, and vaginal biopsy. EFdA IVRs (4.6-10.3 mg/kg EFdA) were administered to 3 female NHP; and EFdA was quantified in plasma and vaginal tissues and fluids and EFdA triphosphate (tp) in PBMCs over 28 days of insertion then 3 days after removal. IVR safety was assessed ex vivo by a vaginal microbiome (VMB) system and in the vaginal epithelial cell (VEC) culture system.

**Results:** Plasma EFdA concentrations of 1-10 ng/mL were maintained over 14 days in sheep and 28 days in NHP. EFdAtp was quantifiable in all 3 NHP over the observation window with all 3 NHP exhibiting EFdAtp concentrations above the therapeutic target for humans (50 fmol/10^6 cells). EFdA concentrations in vaginal tissues were 10-10^3 ng/g in sheep and 10^3-10^5 ng/g in NHP. In sheep, plasma EE (0.01-0.05 ng/mL) and ENG (0.3-0.9 ng/mL) were maintained over 14 days. Vaginal fluid concentrations of EE (1-10 ng/mL) and ENG (10-100 ng/mL) were comparable to NuvaRing® concentrations in sheep. MPT IVRs were well tolerated in sheep and did not induce mucosal disruption or epithelial thinning. These IVRs were also well tolerated in NHP and had no significant impact on cell health in VEC cultures and transplanted VMB. Sheep VMB were also unaffected.

**Conclusion:** We report the first 3D printed EFdA/EE/ENG MPT IVR and demonstrated sustained drug release over >150 days in vitro, 14 days in sheep, and 28 days in NHP. IVRs were well tolerated in vivo (sheep and macaque) and ex vivo (VMB and VEC). Next studies include improved IVR design with modeling, to optimize API dose and release rates for best PK and efficacy outcomes.




G

| Fluids (ng/swab) | Day 3 (ng/swab) | | | Day 7 (ng/swab) | | | Day 14 (ng/swab) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Vaginal (proximal) | Vaginal (distal) | Rectal | Vaginal (proximal) | Vaginal (distal) | Rectal | Vaginal (proximal) | Vaginal (distal) | Rectal |
| Macaque | 16878 | 182111 | 121 | 1307 | 525 | 12.1 | 503 | 217 | 6.86 |

**(A)** In vitro release of EFdA/EE/ENG in simulated vaginal fluid (SVF, sheep pH 7); **(B-C)** EFdA concentrations in sheep plasma and tissue samples; **(D-F)** EFdA & EFdAtp concentrations in pigtailed macaque plasma/PBMCs and tissue samples; **(G)** Median values for EFdA concentration in vaginal and rectal fluids for macaques. IVRs were removed at day 14 and 28 post administration in sheep and macaques respectively. ***(D, E, F)** Green shaded region on graph denotes effective EFdAtp concentrations for humans after oral dosing (50 fmol/10⁶ cells).

## 446 LONG-ACTING DORAVIRINE FOR TREATMENT AND PREVENTION OF VAGINAL HIV TRANSMISSION

**Martina Kovarova**[1], Manse Kim[1], Sarah E. Wessel[1], J. Victor Garcia-Martinez[1]
[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** Non-adherence to HIV treatment is an important health care problem with subsequent development of drug resistance and disease progression. Doravirine (DOR) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with high activity against both wild-type virus ($IC_{50}$ 5.2ng/ml) and the most prevalent NNRTI-resistant HIV variants. We developed injectable long-acting (LA) formulations of DOR that form an implant after subcutaneous administration, can deliver drug >4 months and can be removed to stop drug delivery. Importantly, DOR delivered in this way efficiently suppresses systemic HIV infection and prevents vaginal HIV transmission.

**Methods:** Extended release of DOR from optimized LA-DOR formulations was assessed in BALB/c mice (n=4 per formulation). Tissue drug levels in selected tissues including lymph nodes, spleen, vagina, cervix, uterus, rectum, ileum, and brain were evaluated 5 weeks post administration. Ability to suppressed established HIV infection in plasma and cervicovaginal secretions (CVS) was assessed in BLT mice infected with transmitted/founder HIVRHPA (n=3). Efficacy to prevent HIV vaginal transmission was evaluated using BLT humanized mice treated with LA-DOR (n= 8) or placebo (n=5). BLT mice were vaginally challenge with HIVRHPA 2, 4 and 6 weeks post LA-DOR administration. Peripheral blood was collected weekly and analyzed for HIV-RNA, CD4 T cells, and drug levels. Twelve weeks post administration (4 weeks after the last challenge), LA-DOR implants were removed to stop drug delivery and viremia was monitored for additional 4 weeks.

**Results:** Two LA-DOR formulations provided DOR plasma concentrations >10x$IC_{50}$ for 16 weeks. Median (range) tissue DOR concentrations five-weeks post injection were: vagina 206 ng/g (38.2-229), cervix 271.2 ng/g (42.5-336), uterus 122.3 ng/g (51.6-157), ileum 778.5 ng/g (177-808), rectum 391.4 ng/g (95.2-567), spleen 224.3 ng/g (44.7-351), lymph nodes 281 ng/g (54.4-374), and brain 18.1 (12.9-20.1). LA-DOR suppressed established HIV infection in plasma and CVS in all treated mice. When used for pre-exposure prophylaxis, 4 of 5 controls administered with placebo became infected compared to 1of 8 LA-DOR treated animals. After implant removal, no additional viremia was identified in LA-DOR treated mice.

**Conclusion:** The LA-DOR formulation can deliver drug for four months after a single subcutaneous injection, penetrate to relevant tissues and efficiently prevent vaginal HIV transmission after multiple HIV challenges.

## 447 EVG/COBI/FTC/TAF TABLETS DISSOLVED IN TAP WATER NEAR BIOEQUIVALENT WITH WHOLE TABLETS

**Craig W. Hendrix**[1], Edward J. Fuchs[1], Mark Marzinke[1], Sandra Abdul Massih[1], Jennifer Breakey[1], Sasha Beselman[1], Ian McNicholl[2], Adriana Andrade[3]
[1]*The Johns Hopkins University, Baltimore, MD, USA,* [2]*Gilead Sciences, Inc, Foster City, CA, USA,* [3]*National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

**Background:** Medication adherence can be challenging for persons with pill aversion, dysphagia, odynophagia, or problems swallowing tablets. To provide an alternate to whole Genvoya tablets, we investigated the bioequivalence of a dissolved tablet when compared to a whole tablet of Genvoya, a fixed-dose combination Elvitegravir (EVG)/Cobicistat (COBI)/Emtricitabine (FTC)/Tenofovir (TFV) Alafenamide Fumarate (TAF).

**Methods:** A within-subject, fixed-order, two-period, open label study was conducted in 12 healthy volunteers after obtaining informed consent. HIV negative research participants took a single dose each of the whole tablet and dissolved tablet under direct observation, separated by a 14-day washout period. The dissolved tablet was prepared by adding one whole Genvoya tablet to 120 mL tap water and stirring for dissolution to occur. Both dosage types were taken with a standardized meal. Fifteen plasma samples were obtained pre- and up to 72 h post-dose. Plasma concentrations of EVG, FTC, TAF, and TFV were analyzed with validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) methods. Pharmacokinetic (PK) parameters were analyzed with WinNonlin software (v.8.3) to obtain maximum plasma concentration ($C_{max}$) and the area under the concentration-time curve extrapolated to infinity (AUC0-∞). The primary outcome was bioequivalence consistent with FDA guidance using the 90% confidence interval or the geometric mean ratio (GMR).

**Results:** Of 12 participants, 7 were African American (58 %) and 5 were white (42%), 4 were female (33%), 8 were male (67%), and the mean age was 43.6 (23-54). There were no complaints about taste with the dissolved tablet. Full Bioequivalence was established only for FTC (Table). EVG $C_{max}$ and AUC0-inf were lower by 15% and 11%, respectively, when taking the dissolved formulation compared to the intact tablet. For both TAF and TFV, AUC0-inf met bioequivalence criteria, but the $C_{max}$ GMR upper 90% confidence bound fell above the upper bioequivalence bound.

**Conclusion:** Genvoya rapidly dissolved in water and had no unpleasant taste when swallowed. EVG had a clinically insignificant reduction in concentrations (<15%) while TAF and TFV concentrations did not decline when taking a dissolved Genvoya dose. Dissolving Genvoya in water may be suitable for those with pill swallowing challenges.

| Analyte | $C_{max}$ | | $AUC_{0-inf}$ | |
|---|---|---|---|---|
| | GMR (90% CI) Tablet/Dissolved | Bioequivalence | GMR (90% CI) Tablet/Dissolved | Bioequivalence |
| EVG | 0.85 (0.74, 0.97) | No | 0.89 (0.82, 0.96) | Yes |
| FTC | 1.07 (0.92, 1.24) | Yes | 1.05 (0.99, 1.11) | Yes |
| TAF | 1.09 (0.82, 1.46) | No | 1.07 (0.93, 1.22) | Yes |
| TFV | 1.09 (0.91, 1.30) | No | 1.04 (0.96, 1.14) | Yes |

## 448 TRANSFORMATION OF DOLUTEGRAVIR INTO A YEAR-LONG PARENTERAL PRODRUG FORMULATION

New Investigator Scholar

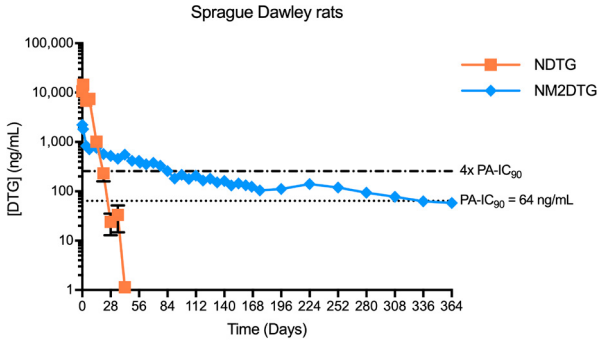
**Suyash Deodhar**[1], Brady Sillman[1], Aditya Bade[1], Brandon Hanson[1], Bhagya Dyavar Shetty[1], Nagsen Gautam[1], JoEllyn McMillan[1], Morgan Johnston[1], Michellie Thurman[1], Yazen Alnouti[1], Samuel M. Cohen[1], Bhavesh D. Kevadiya[1], Siddappa N. Byrareddy[1], Benson J. Edagwa[1], Howard E. Gendelman[1]
[1]*University of Nebraska Medical Center, Omaha, NE, USA*

**Background:** Antiretroviral therapy (ART) requires lifelong daily dosing to attain durable viral suppression. However, regimen adherence dictates effective long-term clinical response by precluding viral rebound. To improve ART effectiveness and ensure adherence, long-acting injectables of cabotegravir and rilpivirine (CAB and RPV LA) were developed. Nonetheless, limitations include high injection volumes, limited drug tissue distribution, and frequent administrations have limited their utility. Intending to prolong the apparent half-life of ART, our laboratories developed prodrug libraries encased in biocompatible surfactants. Herein, we report the characterization of one of these for dolutegravir (DTG). A prodrug library for DTG was characterized then screened for sustained plasma concentrations and tissue biodistribution. The goal was to achieve DTG levels at or above the protein-adjusted (PA) $IC_{90}$ of 64 ng/mL after a single intramuscular (IM) injection for a year or longer.

**Methods:** A prodrug library of DTG was synthesized by esterification using aliphatic lipid chains. This yielded 14 (MDTG), 18 (M2DTG), and 22 (M3DTG) carbon-modified lipophilic prodrugs. A 18 carbon prodrug carrying two DTG molecules on a lipid chain and native DTG completed the drug library. Solid prodrug nanoparticles in aqueous suspension were manufactured by high-pressure homogenization. Particle size, homogeneity, and the surface charge were assessed prior to human monocyte-derived macrophage (MDM) uptake, retention, cytotoxicity, and antiretroviral activity assays. A single 45 mg DTG-equivalents/kg IM dose of prodrug formulations was administered to Balb/cJ mice, SD rats and rhesus macaques. Release and hydrolysis profiles of NM2DTG were investigated.

**Results:** NM2DTG was retained and provided protection beyond 30 days in cultured MDM challenged with HIV-1ADA at a multiplicity of 0.1 infectious particles. A single intramuscular injection of NM2DTG elicited DTG levels at or

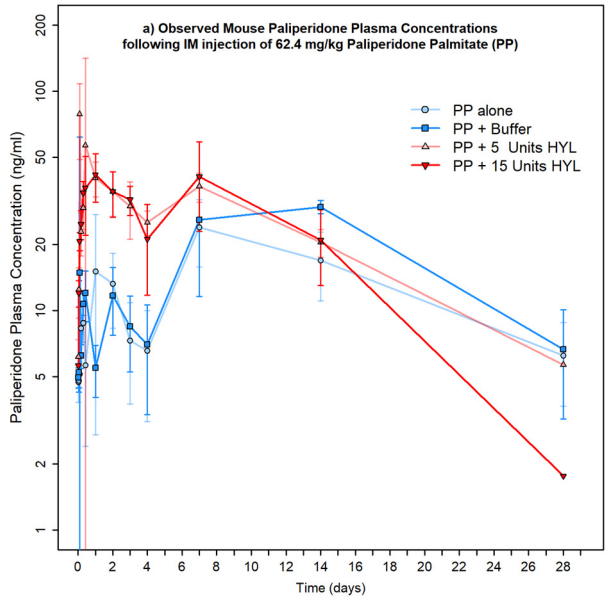
above the PA-$IC_{90}$ for one year in rodents. Replicate PK profiles were recorded in rhesus macaques. Rat spleen, lymph node, liver, and muscle tissues showed 72, 74, 58.5, and 1.1x10^6 ng/g of DTG prodrug at a year. The observed extended PK profile of NM2DTG was linked to prodrug nanocrystal tissue dissolution and pH.
**Conclusion:** The extended NM2DTG PK profile paralleled nanocrystal dissolution and pH-dependent prodrug activation. NM2DTG produced plasma DTG levels at or above the PA-$IC_{90}$ for one year following a single intramuscular injection in rodents.

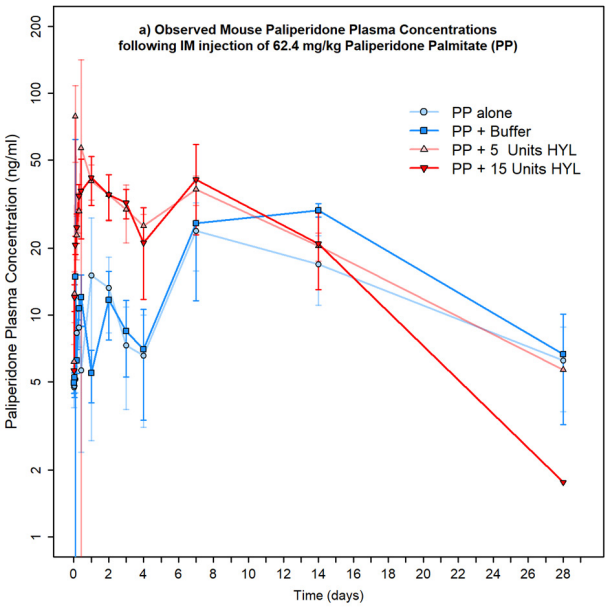



## 449 IMPACT OF HYALURONIDASE ON LONG-ACTING DRUG RELEASE PHARMACOKINETICS IN MURINE MODELS

**Henry Pertinez**[1], Amit Kaushik[2], Paul Curley[1], Usman Arshad[1], Eman El-Khateeb[1], Si-Yang Li[2], Charles W. Flexner[2], Eric Nuermberger[2], Andrew Owen[1], Nicole C. Ammerman[2]
*[1]University of Liverpool, Liverpool, UK, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** Developing long-acting injectable formulations (LAI) of drugs for prevention/treatment of HIV and tuberculosis is of great interest. A key issue in LAI development is the injection volume needed to sustain drug exposure. Co-administration of the extracellular matrix-degrading enzyme hyaluronidase (HYL) can increase maximum tolerable injection volume and is untested for this benefit for any LAI (eg, LAI cabotegravir). Modulation of the tissue response surrounding an injection depot by HYL however may impact drug release kinetics and pharmacokinetic (PK) profiles of LAI. This pilot study aims to test the impact of HYL on the PK of the example LAI paliperidone palmitate (PP) in a mouse PK model.
**Methods:** BALB/c mice were dosed in groups as follows: intramuscular (IM) injection of PP alone; IM of PP plus buffer; IM of PP + 5 units HYL; IM of PP + 15 units HYL; Intravenous (IV) injection of paliperidone (PAL) 3.5 mg/kg (all IM doses at 62.4 mg/kg). Plasma samples were taken serially post dose (4 mice/arm/timepoint) and were analysed for PAL concentration by LC-MS. IV PK was used for deconvolution of the IM PK profiles to aid fitting of a PK model to describe the data and to determine % bioavailability, F.
**Results:** Observed PAL plasma concentrations (mean +/- sd) are shown in figure 1a), and PK model fittings to the data in figure 1b). Deconvolution of the IM PK profiles suggested 2 parallel release processes from the injection site depot, with the 2nd process incorporating a lag-time. Co-administration of HYL appears to increase exposure in the 1st week of the timecourse (AUC0-7d and $C_{max}$ both ~2.5x greater with HYL present) with similar effect for either 5 or 15 units HYL.
**Conclusion:** In this model, co-administration of HYL alters depot release of PAL in the 1st week following IM injection, increasing plasma exposure, but HYL does not negate the long-acting release nature of this dosing route and formulation, with prolonged exposure still maintained for 28 days. Safety/tolerability issues related to increased exposure in week 1 need further investigation, however HYL may have promise for favourable modification of the injection volume of anti-infective LAIs, such as cabotegravir/rilpivirine. Dual depot release rates suggested by the data, with potential modulation by HYL, are consistent with mechanistic descriptions of depot release processes involving resident phagocytic immune cells. Future work will explore histopathology of depot sites +/- HYL and effects of increased dosing volume.



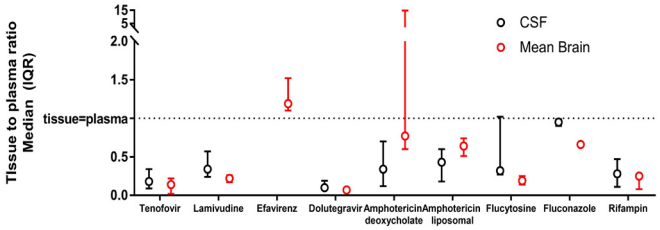




## 450 POSTMORTEM TISSUE SAMPLING TO DESCRIBE EXPOSURE OF 8 ANTI-INFECTIVES IN THE BRAIN

**Melanie R. Nicol**[1], Olivie C. Namuju[2], Katelyn A. Pastick[1], Kizito Abdusalaamu[2], James Fisher[1], Lindsey B. Collins[1], David R. Boulware[1], David Meya[3], Robert Lukande[3]
*[1]University of Minnesota, Minneapolis, MN, USA, [2]Infectious Disease Institute, Kampala, Uganda, [3]Makerere University, Kampala, Uganda*

**Background:** The central nervous system (CNS) is a significant reservoir for pathogens including HIV, Cryptococcus, and tuberculosis. Under exposure in the CNS of drugs used to treat these infections can lead to ineffective treatment and pathogen persistence, while over-exposure can lead to neurotoxicity. Current understanding of drug penetration into the CNS is limited and largely based on cerebrospinal fluid (CSF) concentrations. However, CSF is not brain tissue. Herein we used tissues collected post-mortem from Ugandan subjects with HIV to characterize the relative distribution of 4 antiretrovirals, 3 antifungals, and rifampin across plasma and CNS compartments.
**Methods:** We obtained written, informed consent from next of kin and performed post-mortems on individuals co-infected with HIV, collecting whole blood, CSF, and multiple tissues from CNS; tissues were snap frozen in liquid nitrogen at time of autopsy. Following tissue homogenization, we measured drug concentrations in plasma, CSF, and tissue using liquid chromatography coupled with triple quadrupole mass spectrometer.

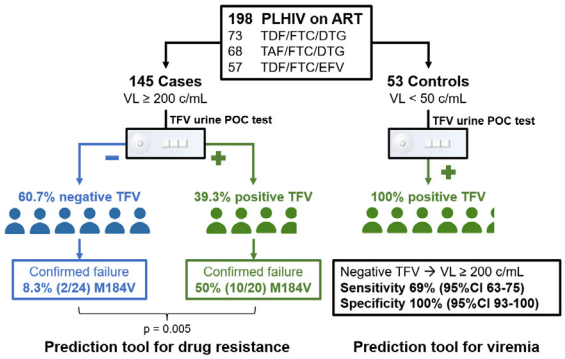
**Results:** We performed post-mortems on 65 individuals with HIV infection who were receiving anti-infective therapy at time of death. Figure 1 shows concentrations relative to plasma for tenofovir (CSF n= 38, tissue n= 11), lamivudine (CSF n=45, tissue n=13) efavirenz (CSF n=4), dolutegravir (CSF n= 16, tissue n= 6), fluconazole (CSF n= 34, tissue n= 8), amphotericin (CSF n= 17, tissue n= 8) flucytosine (CSF n= 13, tissue n= 2) and rifampin (CSF n= 10, tissue n= 3) with concentrations across 12 compartments averaged (mean brain). Brain concentrations were consistently lower than CSF for tenofovir, lamivudine, dolutegravir, and fluconazole while consistently higher than CSF for amphotericin and efavirenz. Concentrations across the 12 compartments were heterogenous, however interindividual variability was greater than intra-individual. Plasma protein binding did not predict penetration into CNS.
**Conclusion:** These data confirm that CSF is a poor surrogate for measuring drug exposure throughout the CNS. Compartments of low drug exposure in the CNS warrant further investigation. Factors in addition to plasma protein binding may be driving distribution into CNS tissues.




## 451 TENOFOVIR URINE POINT-OF-CARE TEST PREDICTS VIREMIA AND DRUG RESISTANCE DURING ART

**Lucas E. Hermans**[1], Chijioke N. Umunakkwe[2], Samanta T. Lalla-Edward[3], Shane Hebel[4], Francois Venter[3], Hugo A. Tempelman[2], Annemarie Wensing[5]
*[1]University of Cape Town, Cape Town, South Africa, [2]Ndlovu Care Group, Groblersdal, South Africa, [3]Ezintsha, University of the Witwatersrand, Johannesburg, South Africa, [4]OraSure Technologies Inc., Bethlehem, PA, USA, [5]University Medical Center Utrecht, Utrecht, Netherlands*

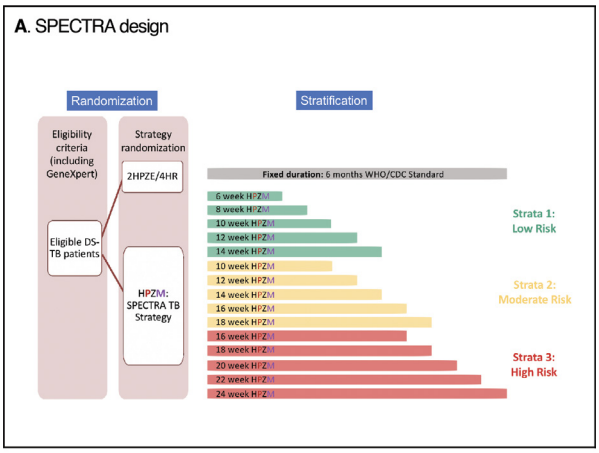
**Background:** Recommended first-line ART in low- and middle-income countries (LMIC) is dolutegravir (DTG), tenofovir disoproxil fumarate (TDF), and lamivudine (3TC) or emtricitabine (FTC) accompanied by annual HIV viral load (VL) testing for treatment monitoring. Viremia during DTG-based ART is often due to suboptimal adherence in the absence of resistance. We hypothesize that qualitative point-of-care (POC) detection of tenofovir (TFV) in urine may predict viremia and improve insight into adherence and drug resistance.
**Methods:** We performed a nested case-control study within the ADVANCE RCT (NCT03122262) in which HIV-infected adults newly initiating ART were randomized to receive either DTG/TAF/FTC, DTG/TDF/FTC or EFV/TDF/FTC. All participants with a VL ≥200 c/mL between 24 and 96 weeks of follow-up on ART were selected as cases. Urine samples from all timepoints with viremia were analyzed. Matched control samples were sourced from participants with VL <50 c/mL. Rapid TFV urine detection (SureQuick Rapid Tenofovir Adherence Test, OraSure Technologies Inc., USA) was performed retrospectively.
**Results:** 281 urine samples from 198 participants (228 samples from 145 cases; 53 samples from 53 controls) were analyzed. Median age was 30 years [IQR: 25–35] and 61.6% were female. Median log VL in cases was 3.4 [2.9–4.3] copies/mL. TFV was positive in 30.7% (70/228) of case samples and in 100% (53/53) of control samples. 39.3% (57/145) of cases had positive TFV on at least 1 sample. Negative TFV predicted VL ≥200 copies/mL (p<0.001) with a sensitivity of 69% [95%CI 63-75] and specificity of 100% [93-100]. In cases with confirmed failure and sequencing data (n=44), NRTI resistance was detected in 50% (10/20) of cases with at least 1 TFV-positive sample versus 8.3% (2/24) of cases with continuously TFV-negative samples. Positive TFV predicted NRTI resistance (OR 10.4 [1.8-114.4] p=0.005) with a sensitivity of 83% [52-98] and specificity of 69% [50-84].
**Conclusion:** Rapid TFV urine detection using a point-of-care test was able to distinguish between virally suppressed and viremic individuals on ART. A negative urine TFV test had high specificity for viremia. In participants with viremia, a positive urine TFV test indicated a higher risk of resistance to the NRTI backbone, which may confer an increased risk of selection of integrase resistance. These results support clinical implementation of POC TFV urine detection to rapidly provide insight into adherence, suppression, and drug resistance during ART in LMIC.

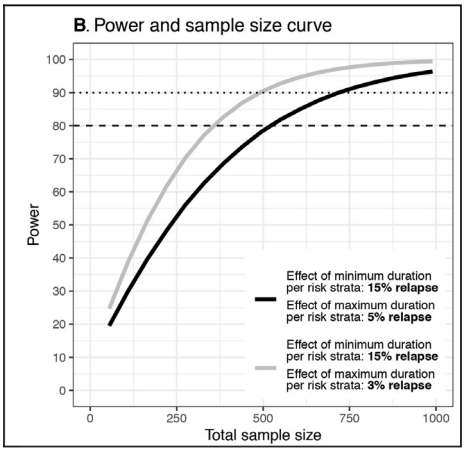



## 452 NOVEL PHASE II TRIAL DESIGN WITH STRATIFIED MEDICINE PRINCIPLES FOR TREATMENT OF TB

**Marjorie Z. Imperial**[1], Vincent Chang[1], Payam Nahid[1], Susan Swindells[2], Gustavo E. Velásquez[1], Rada Savic[1], Patrick P. Phillips[1]
*[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Nebraska Medical Center, Omaha, NE, USA*

**Background:** A5349/S31 showed a 4-month rifapentine-moxifloxacin-based regimen had comparable efficacy to the standard 6-month regimen for the treatment of drug-susceptible tuberculosis (TB). Despite this, we identified subgroups of A5349/S31 participants assigned to the 4-month regimen who were either low-risk and likely did not require 4 months of treatment, or high-risk and experienced unacceptably high relapse rates on the 4-month regimen. Treating all patients with one-size-fits-all regimens is suboptimal. New clinical trials are needed to evaluate stratified medicine approaches for the treatment of TB.
**Methods:** We conducted clinical trial simulations to assess operating characteristics and sample size requirements for a Phase II trial to evaluate optimal durations of the rifapentine-moxifloxacin regimen by risk strata. We used the duration-randomization design whereby participants are randomized to different durations of the same regimen or a fixed duration control regimen. The objective of such a trial would be to demonstrate a duration-response relationship and describe this shape within each risk strata. Using data from A5349/S31, we adapted the MCP-Mod dose-finding methodology for use in duration-finding trials. Nine candidate models for the duration-response relationship were explored, including linear and EMAX models.
**Results:** Five durations for each risk strata would be included in the trial (low risk: 6, 8, 10, 12, 14 weeks; medium risk: 10, 12, 14, 16, 18 weeks; high risk: 16, 18, 20, 22, 24 weeks; Figure A). In A5349/S31, the rifapentine-moxifloxacin regimen had 4%, 6%, and 10% relapse in the low, moderate and high-risk groups, respectively. For a dose-optimized regimen, with the assumption of a combined 15% relapse for the minimum durations of each risk strata (6, 10, and 16 weeks, respectively) and 5% for the maximum durations (14, 18, and 24 weeks, respectively), a sample size of 45 per duration in each risk group (total sample size of 730, accounting for 10% censored observations) provides 90% power to detect a duration-response relationship (Figure B). Alternatively, with a combined 3% relapse for the maximum durations, a sample size of 30 per duration in each risk group (total sample size of 500) provides 90% power to detect a duration-response relationship.
**Conclusion:** Stratified medicine is essential to end the TB epidemic; we describe feasible and practical duration-randomization Phase II trial designs to facilitate prospective evaluation of stratified treatment strategies.




**453 WITHDRAWN**

**454 PHASE-2 STUDY OF SAB-185, A POLYCLONAL ANTIBODY TREATMENT FOR COVID-19 IN ACTIV-2**

Late Breaking

**Babafemi O. Taiwo**[1], Kara W. Chew[2], Mark Giganti[3], David A. Wohl[4], Eric S. Daar[2], Maxine Olefsky[5], Rick Finnegan[6], Jake Miles[6], Arzhang Cyrus Javan[7], Jonathan Li[8], Judith S. Currier[2], Joseph J. Eron[4], Michael Hughes[9], Davey M. Smith[10]

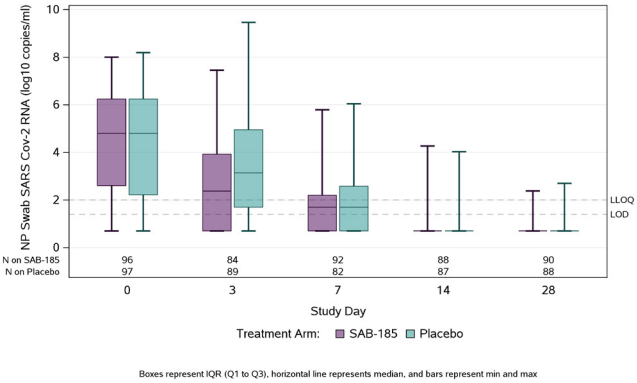
*[1]Northwestern University, Chicago, IL, USA, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]Harvard Medical School, Boston, MA, USA, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [5]Harvard University, Cambridge, MA, USA, [6]SAB Biotherapeutics, MA, USA, [7]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [8]Brigham and Women's Hospital, Boston, MA, USA, [9]Harvard TH Chan School of Public Health, Boston, MA, USA, [10]University of California San Diego, San Diego, CA, USA*

**Background:** The discovery and development of SARS-CoV-2 therapies remains a priority. SAB-185 is a Transchromosomic, bovine-derived, fully human polyclonal immunoglobulin product for SARS-CoV-2 being studied in ACTIV-2, randomized controlled platform trial evaluating the safety and efficacy of investigational agents for non-hospitalized adults with mild-moderate COVID-19

**Methods:** This Phase II trial was a superiority comparison of SAB-185 vs. placebo. Participants with confirmed SAR-CoV-2 infection received intravenous infusion of SAB-185 (3,840 Units/kg) or placebo. Primary outcome measures were proportion of participants with SARS-CoV-2 RNA < lower limit of quantification (LLoQ) in nasopharyngeal (NP) swab, time to improvement in targeted symptoms for 2 consecutive days after Day 0, and safety through Day 28. Secondary outcomes included quantitative NP RNA levels and all-cause hospitalizations and deaths. Antiviral or clinical efficacy and safety criteria for graduation to Phase III were pre-specified.

**Results:** From April to August 2021, randomized participants from 42 sites in the US received SAB-185 (N=107) or placebo (N=106). Median age was 38 years (quartiles: 30,48), 54% female, >98% cis-gender, 7% Black/African-American, 50% Hispanic, and 11% were classified as high-risk for COVID-19 progression, with median 4 days (3,6) from symptom onset. Day 0 NP SARS-CoV-2 RNA levels were similar between SAB-185 and placebo: 4.80 vs 4.80 $\log_{10}$ copies/ml. No differences were observed in the proportion with NP SARS-CoV-2 RNA< lower limit of quantification (LLoQ) in nasopharyngeal (NP) swab, time to improvement in targeted symptoms for 2 consecutive days after Day 0, and safety through Day 28. Secondary outcomes included quantitative NP RNA levels and all-cause hospitalizations and deaths. Antiviral or clinical efficacy and safety criteria for graduation to phase 3 were pre-specified.

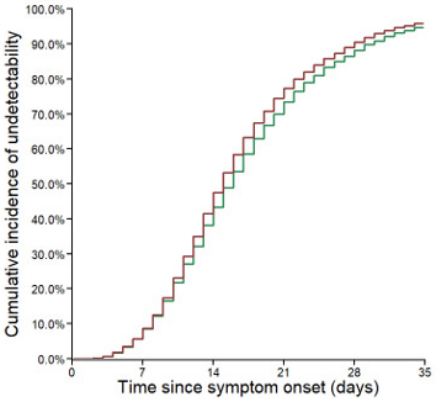
**Conclusion:** SAB-185 was safe in this Phase II study. While no significant differences to placebo were seen in symptom duration and proportion of participants with NP SARS-CoV-2 RNA< lower limit of quantification (LLoQ) in nasopharyngeal (NP) swab, time to improvement in targeted symptoms for 2 consecutive days after Day 0, and safety through Day 28. Secondary outcomes included quantitative NP RNA levels and all-cause hospitalizations and deaths. Antiviral or clinical efficacy and safety criteria for graduation to phase 3 were pre-specified.



## 455 MODELING REMDESIVIR ANTIVIRAL EFFICACY IN COVID-19 HOSPITALIZED PATIENTS

**Guillaume Lingas**[1], Nadège Néant[1], Alexandre Gaymard[2], Drifa Belhadi[3], Maya Hites[4], Dominique Costagliola[5], Yazdan Yazdanpanah[3], Florent Wallet[6], Amandine Gagneux-Brunon[7], France Mentré[1], Florence Ader[6], Charles Burdet[3], Jérémie Guedj[1], Maude Bouscambert-Duchamp[2]
*[1]Université de Paris, IAME, INSERM, Paris, France, [2]Laboratoire de Virologie, Institut des Agents Infectieux de Lyon, Lyon, France, [3]Assistance Publique–Hôpitaux de Paris, Paris, France, [4]Université Libre de Bruxelles, Brussels, Belgium, [5]Sorbonne University, Paris, France, [6]Hospices Civils de Lyon, Lyon, France, [7]Centre Hospitalier Universitaire de Saint Etienne, Saint Etienne, France*

**Background:** Despite several clinical studies, the antiviral efficacy of remdesivir in COVID-19 hospitalized patients remains controversial.
**Methods:** We analyzed nasopharyngeal normalized viral loads collected in the 29 days following randomization from 665 hospitalized patients included in the DisCoVeRy trial, allocated to either standard of care (SoC, N=329) or SoC + remdesivir for 10 days (N=336). We used a mathematical model to reconstruct viral kinetic profiles and estimate the antiviral efficacy of remdesivir in reducing viral production. To identify factors associated with viral kinetics, additional analyses were conducted stratified either on time of treatment initiation (≤ or > 7 days since symptom onset) or viral load at randomization (< or ≥ 3.5 $\log_{10}$ copies/104 cells).
**Results:** In our model, remdesivir reduced viral production by 2-fold on average (95%CI: 1.5-3.2). Using the estimated parameter of the model, simulations predict that remdesivir reduces time to viral clearance by 0.7 day compared to SoC, with large inter-individual variabilities (Inter-Quartile Range, IQR: 0.0-1.3 days). Exploratory analyses suggest that remdesivir had a larger impact on patients with a high viral load at randomization, reducing viral production by 5-fold on average (95%CI: 2.8-25), leading to a predicted median reduction in the time to viral clearance of 2.4 days (IQR: 0.9-4.5 days).
**Conclusion:** Our model shows that remdesivir reduces viral production from infected cells by a factor 2, leading to a median reduction of 0.7 days in the time to viral clearance compared to SoC. The efficacy was larger in patients with high level of viral load at treatment initiation.




## 456 SAFETY OF REMDESIVIR VS PLACEBO IN NONHOSPITALIZED PATIENTS WITH COVID-19

**Bradon Webb**[1], Godson Oguchi[2], Yessica Sachdeva[3], John Cafardi[4], Alan S Go[5], Kavita Juneja[6], Santosh Davies[6], Shuguang Chen[6], Chen-Yu Wang[6], Anu O. Osinusi[6], Frank Duff[6], Pablo Ryan[7], Carlos Vaca[8], Jorge Mera[9]
*[1]Intermountain Healthcare, Murray, UT, USA, [2]Midland Florida Clinical Research Center, Deland, FL, USA, [3]Arizona Liver Health, Mesa, AZ, USA, [4]The Christ Hospital, Cincinnati, OH, USA, [5]Kaiser Permanente, Oakland, CA, USA, [6]Gilead Sciences, Inc, Foster City, CA, USA, [7]Hospital Universitario Infanta Leonor, Madrid, Spain, [8]Nuren Medical and Research Center, Miami, FL, USA, [9]Cherokee Nation Health Services, Talequah, OK, USA*

**Background:** Remdesivir (RDV), a potent nucleotide inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase, effectively reduces COVID-19 related hospitalization in outpatients at high risk for progression to severe disease. However, limited data exist on the safety profile of RDV in this population.
**Methods:** We conducted a Phase III placebo-controlled study evaluating a 3-day regimen of RDV in non-hospitalized patients who are at risk for disease progression (age>60 years or underlying comorbid condition). Patients were randomly assigned 1:1 to receive intravenous RDV (200 mg on day 1, 100 mg on days 2 to 3) or placebo (PBO). The primary safety endpoint was the proportion of patients with treatment-emergent adverse events (AEs). AEs were evaluated through day 28 and lab abnormalities were evaluated through day 14.
**Results:** 562 patients were randomized and initiated treatment (279, RDV; 283, placebo). Baseline characteristics were balanced between groups. Thirty percent were ≥60 years old and most common comorbidities were diabetes mellitus (62%), obesity (56%; median BMI, 30.7 $kg/m_2$), and hypertension (48%). RDV was well tolerated with a similar rate of any AEs between groups (Table). Patients treated with RDV had fewer Grade ≥3 and serious AEs (SAEs) compared to PBO, but had more study-drug related AEs, with the most common one being nausea (18 [6.5%] in RDV vs. 10 [3.5%] in PBO). Grade 3 or higher ALT elevation was reported in 1 (0.4%) RDV vs. 2 (0.7%) PBO treated patients. Median change from baseline in AST, ALT, and bilirubin was similar between groups (Table). Grade 3 or higher decrease in creatinine clearance (CrCl) occurred more often in RDV vs. to PBO treated patients (5.6% vs 1.9% respectively). Most decreases in creatinine clearance occurred within the normal serum creatinine range, occurred after completion of RDV therapy, and resolved on follow-up. Median changes in CrCl from baseline were similar between groups and no renal AEs were reported (Table). Incidence of cardiac-related AEs was similar between RDV and PBO groups. All bradycardia events occurred in the PBO group. No patient experienced a serious AE or drug discontinuation due to hypersensitivity.
**Conclusion:** Treatment with RDV was safe and well tolerated in non-hospitalized patients with risk factors for COVID-19 disease progression. Patients in the RDV group had similar type, incidence, and severity of AEs and lab abnormalities as those receiving PBO.

| | | Remdesivir (N= 279) | Placebo (N=283) |
|---|---|---|---|
| **Any AE, n (%)** | | 118 (42) | 131 (46) |
| **AEs ≥5% in any group** | Nausea | 30 (11) | 21 (7) |
| | Headache | 16 (6) | 17 (6) |
| | Cough | 10 (4) | 18 (6) |
| | Dyspnea | 7 (3) | 15 (5) |
| **Grade ≥3 AE** | | 10 (4) | 20 (7) |
| **Study drug-related AE** | | 34 (12) | 25 (9) |
| **Serious AE** | | 5 (2) | 19 (7) |
| **Study-drug related SAE** | | 0 | 0 |
| **AEs leading to discontinuation** | | 2 (0.7) | 5 (2) |
| **Death** | | 0 | 0 |
| **Grade ≥3 lab abnormalities** | | 29 (11) | 23 (8) |
| **Renal and Hepatic Lab Parameters** Change from Baseline at day 14 in ALT U/L, median (IQR) | | -1 (13) | -1 (14) |
| Change from Baseline at day 14 in AST U/L, median (IQR) | | -3 (11) | -2 (8) |
| Change from Baseline at day 14 in Bilirubin U/L, median (IQR) | | 0.1 (0.2) | 0.1 (0.2) |
| Change from Baseline at day 14 in CrCl U/L, median (IQR) | | 1.75 (18.1) | 1.8 (18.9) |

## 457 EFFECTS OF CASIRIVIMAB + IMDEVIMAB ON SYMPTOM OUTCOMES IN OUTPATIENTS WITH COVID-19

**Yuhuan Wang**[1], Mohamed Hussein[2], Diana Rofail[2], Kuan-Ju Lin[2], Daniela J. Conrado[2], Kenneth C. Turner[2], Samit Ganguly[2], Hazem E. Hassan[2], Qian Huang[2], Zhichao Lyu[2], Hong Yan[2], Thomas Norton[2], Shazia Ali[2], John D. Davis[2], Nidal Al-Huniti[2]
*[1]Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA*

**Background:** Symptoms reduction is a crucial outcome to be considered when testing novel treatments for COVID-19. The goal was to assess the impact of casirivimab+imdevimab (cas+imd) dose/exposure on the trajectory and resolution time of symptoms in outpatients with COVID-19.
**Methods:** Analysis used data from the COV-2067 trial (NCT04425629). Cas+imd was administered intravenously (total dose 1.2 to 8 g). Symptoms data were collected using SE-C19, a patient-reported survey developed de novo to assess the symptomatic course of COVID-19. Based on patients' responses on SE-C19, a Rasch analysis was used to derive a latent score to infer their overall underlying symptom severity. A direct response model was fitted to the latent score-

time data to quantify the effects of dose/exposure, demographic and clinical characteristics on latent symptom trajectory. Symptoms resolution time was defined as time from randomization to the 1st day during which the patient scored "no symptom". Several parametric models were tested as structural model, assuming a known distribution, eg, exponential or Weibull, for time to symptoms resolution data. Risk variables (eg, binary treatment or categorical dose levels, exposure metrics, baseline demographic, clinical, and biological characteristics) were tested as covariates using a proportional hazard model.
**Results:** Results from the direct response model suggest that each dose, as compared to placebo, remarkably reduced IT50 (time taken to achieve half of the maximal response of reducing symptom) by ~40%. By excluding data from placebo arm, none of the tested doses or predicted exposures, were significant covariates on any of the model parameters. Results from the parametric regression analysis further confirmed that cas+imd (HR=1.25) is a major factor shortening the symptoms resolution time in a dose- and exposure-independent manner. Males (HR=1.13) have a shorter symptoms resolution time. Older age (HR=0.991), higher BMI (HR=0.988), and more severe baseline symptoms (HR=0.783 for moderate and 0.589 for severe) significantly contribute to longer symptoms resolution time.
**Conclusion:** Treatment with cas+imd (1.2 g or above), rapidly resolved symptoms in outpatients in a dose- and exposure-independent manner as indicated by a direct response model using derived latent score and further confirmed by a survival analysis using time to symptoms resolution. In addition, symptom severity, age, BMI, sex were major risk factors affecting the symptoms resolution time.

## 458 REMDESIVIR IN AN OUTPATIENT SETTING IMPROVES BIOMARKERS FOR PROGRESSION OF COVID-19

**David Z. Pan**[1], Pamela Odorizzi[1], Andre Schoenichen[1], Mazin Abdelghany[1], Shuguang Chen[1], Chris Blair[1], Henry N. Hulter[1], Scott D. Patterson[1], Anu O. Osinusi[1], Kavita Juneja[1], Jeffrey Wallin[1]
*[1]Gilead Sciences, Inc, Foster City, CA, USA*

**Background:** There is currently no approved treatment for patients with COVID-19 who have not been hospitalized, a setting in which early intervention may curb progression to more severe disease requiring hospitalization. We report longitudinal biomarker sampling from a Phase III (PINETREE) clinical trial to evaluate prognostic biomarkers of COVID-19 and to better understand the early remdesivir (RDV) treatment response.
**Methods:** A Phase III, randomized, double-blind, placebo controlled, multicenter study was conducted to evaluate the efficacy and safety of RDV for outpatients with early stage COVID-19 who are at higher risk of disease progression (NCT04501952). Inclusion criteria were ≥60 years of age or ≥12 years of age with at least one risk factor for severe COVID-19 disease. All individuals had ≤7 days of symptoms prior to randomization. A total of 562 participants were randomized 1:1 to RDV or placebo. Serum and plasma were collected for biomarker analyses in 312 patients at days 1, 3, and 14 post-treatment. All biomarker values were adjusted for baseline age and stratified by sex.
**Results:** RDV demonstrated an 87% reduction in risk for the primary composite endpoint of COVID-19-related hospitalization or all-cause death by day 28 (0.7% [2/279]) compared with placebo (5.3% [15/283]) (p=0.008). RDV treatment was associated with improved clinical outcomes in participants with higher risk of hospitalization or death from COVID-19, including individuals ≥60 years of age, males, and/or those with diabetes, obesity, and hypertension. Furthermore, we found that biomarkers associated with inflammation and coagulation, including lactate dehydrogenase (p<0.001) and procalcitonin (p<0.001), were prognostic for COVID-19 related hospitalization or all-cause death by day 28. Finally, we found that RDV improved some biomarkers associated with COVID-19 severity by day 3 of treatment, including peripheral lymphopenia, monocyte count, and decreased neutrophil-to-lymphocyte ratio compared to placebo (pWilcox<0.05).
**Conclusion:** Our findings suggest that RDV treatment improves COVID-19 outcomes in high-risk SARS-CoV-2 infected individuals, particularly in those ≥60 years of age, male, and/or with diabetes, obesity, and hypertension. Biomarkers of COVID-19 severity that were prognostic for poor outcomes were identified in early infection. Furthermore, our results suggest that RDV treatment leads to more rapid recovery in the lymphopenia that is commonly associated with more severe COVID-19.

## 459 A RANDOMIZED CONTROLLED TRIAL OF CAMOSTAT IN OUTPATIENTS WITH COVID-19

**Nikolaus Jilg**[1], Janet Nuttall[2], Atasi Jana[3], David Maislin[4], Susan Lewis[3], Bob Szurgot[3], Philip A. Hart[5]
*[1]Massachusetts General Hospital, Boston, MA, USA, [2]Kangen Pharmaceuticals, America LLC, Kansas City, KS, USA, [3]Sagent Pharmaceuticals, Schaumburg, IL, USA, [4]Biomedical Statistical Consulting, Philadelphia, PA, USA, [5]The Ohio State University, Columbus, OH, USA*

**Background:** Camostat, an oral protease inhibitor, blocks entry and replication of SARS-CoV-1 and SARS-CoV-2 in vitro. It is approved for therapy of recurrent pancreatitis in several countries. Camostat has an excellent safety profile and repurposing for COVID-19 treatment was proposed.
**Methods:** We conducted a Phase II randomized, placebo-controlled trial of camostat in adult outpatients with confirmed COVID-19 and one or more risk factors for severe disease (including age ≥65 years, severe obesity, hypertension, diabetes, chronic lung, heart or liver disease). Participants were randomized 2:1 to oral camostat 200 mg or matching placebo four times a day for 14 days. Exclusion criteria were end-stage liver disease, severe renal impairment, oxygen saturation ≤94% on room air, and experimental treatment for COVID-19. The primary efficacy endpoint was hospitalization or death within 28 days. Secondary efficacy included positivity for SARS-CoV-2 by PCR on mid-nasal turbinate swabs on days 7 and 15 compared to baseline.
**Results:** We enrolled 295 participants, 57.3% were female, 15.6% Black and 60% Latinx. Mean age was 51 years (18-93 years). Most (75.3%) were randomized ≤5 days after symptom onset. Common risk factors were hypertension (63.4%), chronic lung disease (33.2%) and diabetes (25.4%), with 46.8% having >1 risk factor. With a lower than anticipated event rate, the primary endpoint of hospitalization or death was not significantly different in the camostat (5.3%, 10/194) and placebo groups (6.1%, 6/99; p=0.78). In the intention-to-treat population, there was a trend towards a lower proportion of PCR positivity in the camostat compared to the placebo group at day 7 (65.2% vs. 75.7%, p=0.12) and day 15 (22.0% vs. 34.3%, p=0.06). Similarly, in a post hoc as treated population, fewer participants in the camostat than in the placebo group remained PCR positive at day 7 (64.7%, 88/136 vs. 76.8%, 53/96; p=0.077) and day 15 (21.8%, 29/133, vs. 34.8%, 23/66; p=0.05). Adverse events occurred in 13% of participants in the placebo and 9% in the camostat group. All severe adverse events (5% in both groups) were related to COVID-19.
**Conclusion:** With a low overall event rate, we did not observe a decrease in risk of hospitalization or death in camostat treated outpatients with COVID-19 at risk for severe disease. SARS-CoV-2 PCR turned negative faster on camostat treatment. Camostat was well tolerated.

## 460 TDF/FTC FOR HIGH-RISK PATIENTS WITH COVID-19: THE PANCOVID RANDOMIZED CLINICAL TRIAL

**María Velasco**[1], Rocio Montejano[2], Gonzalo Sierra[1], Javier Queiruga[2], Patricia Martínez[3], Ane Goikoetxea[4], Angela Gutierrez[5], Miguel Torralba[6], Pablo Ryan[7], Pilar Vizcarra[8], Sofía Ibarra[9], Maria Jimenez-Gonzalez[10], Javier Marcos[1], Jose R. Arribas[2]
*[1]Hospital Universitario Fundación Alcorcón, Alcorcón, Spain, [2]La Paz University Hospital, Madrid, Spain, [3]Hospital Infanta Sofía, Madrid, Spain, [4]Hospital Universitario de Cruces, Baracaldo, Spain, [5]Hospital Universitario de La Princesa, Madrid, Spain, [6]Hospital Universitario de Guadalajara, Guadalajara, Spain, [7]Hospital Universitario Infanta Leonor, Madrid, Spain, [8]Hospital Ramón y Cajal, Madrid, Spain, [9]Hospital de Basurto, Basurto, Spain, [10]Hospital La Paz Institute for Health Research, Madrid, Spain*

**Background:** Some in vitro, animal, and epidemiological data suggest that tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) might be an efficacious treatment for COVID-19
**Methods:** In a multicenter open-label, pragmatic, randomized trial in 25 hospitals in Spain we included participants with symptomatic SARS-CoV-2 detected by PCR or antigenic test, with a creatinine clearance > 60 mL/min, > 60 years or younger if they had at least 2 comorbidities (hypertension, obesity, diabetes, cirrhosis, chronic neurologic disease, active cancer, heart failure, coronary heart disease or COPD). Participants were randomized to receive or not TDF/FTC. Randomization was stratified by age group, symptoms duration (< or ≥ 5 days) and health care setting (hospitalized, long-term care facility, ambulatory). Primary outcome was 28 days mortality. Secondary outcomes were disease progression (increased O2 requirements, need for mechanical

ventilation or increase in medical therapy: steroid dose, need for tocilizumab). At any moment during the trial participants with room air O2 saturation < 95% and ≥ 1 increased inflammatory biomarker could be randomized to dexamethasone (D) or dexamethasone plus baricitinib (DB)
**Results:** 355 participants included (TDF/FTC n=177, no TDF/FTC n=178), median age 67 years (IQR 62-73), male (64.5%), median days of symptoms 8 (IQR 5-10), 29% with < 5 days of symptoms, 96.9% hospitalized, 35.5% with 1 and 36.6 % with ≥ 2 comorbidities (62.8% hypertension, 9.3% diabetes, 1.7% obesity), median room air SaO2 95% (IQR 94-96), 63% receiving O2 and 11.8% Remdesivir. 74% of participants were simultaneously randomized to D or DB. There were not statistically significant differences in endpoints in participants not treated vs.treated with TDF/FTC: mortality 2.2%/4.0%, disease progression 23.6%/22.0%, deferred randomization to D or DB 6.7%/6.2%, mechanical ventilation (invasive or noninvasive) 22.5%/20.3%, days since randomization until discharge (median [IQR]) 7 [5,14]/6 [4,12], discharge before 28 days 91.9%/89.7%. By Cox regression Hazard Ratio (95% CI) of 28-day mortality was 1.96 (0.55-7.01) for participants treated with TDF/FTC. Serious adverse events occurred in 6.18%/5.65% of participants not treated/treated with TDF/FTC. Adverse events leading to TDF/FTC discontinuation occurred in 2.26%.
**Conclusion:** In this clinical trial of high-risk patients with COVID-19 TDF/FTC did not improve disease outcomes. Overall mortality was unexpectedly low

## 461 VIRAL KINETICS IN COVID-19 OUTPATIENTS TREATED WITH CASIRIVIMAB+IMDEVIMAB COMBINATION

**Daniela J. Conrado**[1], Kashyap Patel[2], Kuan-Ju Lin[1], Yuhuan Wang[1], Jiraganya Bhongsatiern[1], Mohamed A. Kamal[1], Kenneth C. Turner[1], Samit Ganguly[1], Hazem E. Hassan[1], Hong Yan[1], Cynthia Portal-Celhay[1], John D. Davis[1], Patrick F. Smith[2], Jérémie Guedj[3], Nidal Al-Huniti[1]
*[1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, [2]Certara, Princeton, NJ, USA, [3]Université de Paris, Paris, France*

**Background:** Casirivimab+imdevimab (hereinafter referred to as drug) remains vital in reducing hospitalization/death by 70% when administered early in the course of the infection. Our aim was to illustrate the mechanism of drug action in vivo and determine the magnitude of antiviral efficacy of various dose regimens given to outpatients with COVID-19, evaluating the presence of SARS-CoV-2 sero-antibody and ≥1 high-risk factor for developing severe COVID-19 illness as predictors of viral kinetics.
**Methods:** Analysis data came from 2 clinical studies in SARS-CoV-2 infected outpatients with no or ≥1 risk factor for severe COVID-19 (NCT04425629 and NCT04666441), who received single dose of placebo or drug IV (300mg to 8g) or SC (600mg to 1.2g), had assessed viral load in nasopharyngeal swab and drug concentrations in serum (N=4500). The median number of viral load assessments per patient was 5 (range 1-8) within up to 14 days of follow-up time. Drug concentrations were predicted using the individual pharmacokinetic parameters yielded by a population model. The median patient age was 42 years, with similar proportion of males and females. The median viral load at baseline was 6.79 $\log_{10}$ copies/mL, and the median time of symptom onset was 3 days before study baseline. A standard target cell-limited model was used to estimate the time of infection and reconstruct viral kinetic profiles. Various relationships between exposure and resulting antiviral response were evaluated, where the drug could block de novo infection, increase the elimination rate of infected cells, or reduce viral production from infected cells.
**Results:** The results support that the main mechanism of drug action is blocking de novo infection with an estimated decrease in the infectivity rate of 96.6%, for all dose regimens evaluated herein. High-risk factor for severe COVID-19 and baseline sero-antibody-positive/other status were associated with a 4.71% decrease and a 4.96% increase in the elimination rate of infected cells, respectively. The estimated median and 95th percentile of time to viral clearance (ie, viral count reaches below assay quantification limit) were 1.4 and 3.4 days shorter in drug vs placebo (median 10.6 vs 12.0 days, and 95th percentile 15.2 vs 18.6 days).
**Conclusion:** All IV and SC casirivimab+imdevimab dose regimens evaluated herein showed similar near-maximal antiviral activity by blocking de novo infection; hence, shortening the time to virus clearance.

## 462 A REAL-WORLD COMPARISON OF BAM/ETE VS CAS/IMD FOR COVID-19 CLINICAL PROGRESSION RISK

**Valentina Mazzotta**[1], Francesca Colavita[1], Patrizia Lorenzini[1], Alessandro Cozzi-Lepri[2], Silvia Rosati[1], Ilaria Mastrorosa[1], Eleonora Lalle[1], Claudia Cimaglia[1], Alessandra Vergori[1], Angela Corpolongo[1], Concetta Castilletti[1], Enrico Girardi[1], Francesco Vaia[1], Emanuele Nicastri[1], Andrea Antinori[1]
*[1]IRCCS Lazzaro Spallanzani, Rome, Italy, [2]University College London, London, UK*

**Background:** Few data are available about comparison of different monoclonal antibodies (MAbs) for COVID-19 in the real-world setting. We aim to compare effectiveness of bamlanivimab/etesevimab (BAM/ETE) versus (vs) casirivimab/imdevimab (CAS/IMD) and to estimate predictors of hospitalization/death.
**Methods:** Observational analysis of all consecutive outpatients (pts) with mild/moderate COVID-19 enrolled within the AIFA access program in a single center in Rome, from March to October, 2021. At first baseline (BL) visit, RT-PCR from nasopharyngeal swab with cycle thereshold (CT) measurement and viral sequencing was performed. Pts received intravenous BAM/ETE (700/1400 mg) or CAS/IMD (1200/1200 mg) and were followed through day 30. Primary endpoint was hospitalization/death due to severe COVID-19 by day 30. Average treatment effect (ATE) in the multiplicative scale of the odds was the chosen estimand to compare the two treatments, adjusted for age, obesity, time from onset to infusion, median C-reactive protein (CRP), vaccination, variant of concern (VOC) and BL-CT. Predictors of clinical failure were explored by two different models of multivariable logistic regression.
**Results:** 242 pts receiving BAM/ETE (n=76) or CAS/IMD (n=166) were included (male 54%; median age 65 yrs; median SpO2 97%; diabetes 12%; hypertension 40%; CVD 17%; COPD 26%; autoimmune diseases 12%; immunodeficiency 18%). Median time from symptoms onset to infusion was 4 days (IQR 3-6). No differences were observed between the two MAbs for BL characteristics except for BMI>35 (BAM/ETE 24%, CAS/IMD 12%), CRP (BAM/ETE 1.8, CAS/IMD 1.2), vaccination (BAM/ETE 26%, CAS/IMD 46%) and distribution of VOC (Alpha 46% BAM/ETE vs 22% CAS/IMD; Gamma 20% vs 7%; Delta 5% vs 55%). Proportion of patients with COVID-related hospitalization/death by day 30 was 12/76 (15.8%) for BAM/ETE and 6/166 (3.6%) for CAS/IMD. Estimate of causal effect of BAM/ETE exposure compared to CAS/IMD on primary end point by ATE is reported in Table 1a. Factors associated with an increased risk of clinical failure by fitting multivariable logistic regression were BMI >35 and P1/Gamma VOC; higher BL-CT was associated with a reduced risk (Table 1b-1c).
**Conclusion:** In a real-life setting, receiving BAM/ETE was associated with a 4-fold higher risk of COVID-19 progression to hospitalization/death than CAS/IMD. SARS-CoV-2 P.1/Gamma, but not B.1617.2/Delta VOC, obesity and higher BL viral load also predicted an increased risk of clinical worsening.

***Table 1a*** *Average treatment effect (ATE) estimates of causal effect of the two MAbs combo on the primary endpoint of hospitalization/death due to severe COVID-19 by day 30. Data were adjusted for age, BMI≥35, Time from onset, CRP, SARS-COV-2 vaccination, VoC, BL-CT.*

| | UNWEIGHTED | | | WEIGHTED | |
|---|---|---|---|---|---|
| **MAbs combo** | **OR** | **95%CI** | **p-value** | **OR** | **95%CI** |
| BAM/ETE | 5.00 | 1.8-13.89 | 0.002 | 4.34 | 3.44-24.06 |
| CAS/IMD | 1.00 | | | | |

***Table 1b*** *Association between CT, obesity and risk of hospitalization/death*

| | UNADJUSTED | | | ADJUSTED* | | |
|---|---|---|---|---|---|---|
| | **OR** | **95%CI** | **p-value** | **OR** | **95%CI** | **p-value** |
| Obesity (BMI≥35 vs <35) | 4.44 | 1.54-12.80 | 0.006 | 5.11 | 1.15-22.67 | 0.032 |
| Baseline CT, per higher unit | 0.78 | 0.67-0.91 | 0.002 | 0.69 | 0.54-0.87 | 0.002 |

**adjusted for age, vaccination, duration of symptoms, CRP, type of MAbs exposure and SARS CoV2 variant*

***Table 1c*** *Association between VoC and risk of hospitalization/death*

| | UNADJUSTED | | | ADJUSTED* | | |
|---|---|---|---|---|---|---|
| | **OR** | **95%CI** | **p-value** | **OR** | **95%CI** | **p-value** |
| **SARS-COV-2 VARIANT** | | | | | | |
| B.1.1.7/Alpha | 1.00 | | | 1.00 | | |
| P.1/Gamma | 5.96 | 1.74-20.43 | 0.005 | 4.04 | 0.76-21.31 | 0.100 |
| B.1617.2/Delta | 0.59 | 0.15-2.28 | 0.443 | 0.91 | 0.06-14.55 | 0.947 |
| Other/not suitable for sequencing | 0.28 | 0.03-2.47 | 0.251 | 0.67 | 0.06-7.04 | 0.739 |

**adjusted for age, vaccination, duration of symptoms, CRP, type of MAbs exposure and obesity*

## 463 BARICITINIB FOR HIGH-RISK PATIENTS WITH COVID-19: THE PANCOVID RANDOMIZED TRIAL

**Alberto Borobia**[1], Fernando de la Calle[1], Carlos Guijarro[2], Patricia González-Ruano[3], Marta Ibarrola[4], Marianela Ciudad[5], Ana Díaz-Brasero[6], Antonio de Pablo[2], Cristina Marcelo[7], Cristina Díez[8], Esperanza Merino[9], Vicente Estrada[10], María Novella Mena[11], Jose R. Arribas[1]

*[1]La Paz University Hospital, Madrid, Spain, [2]Hospital Universitario Fundación Alcorcón, Alcorcón, Spain, [3]Hospital Universitario Infanta Sofía, Madrid, Spain, [4]Hospital Universitario de Cruces, Baracaldo, Spain, [5]Hospital Universitario de la Princesa, Madrid, Spain, [6]Hospital Universitario de Guadalajara, Guadalajara, Spain, [7]Hospital de Emergencias Enfermera Isabel Zendal, Madrid, Spain, [8]Hospital Universitario Gregorio Marañón, Madrid, Spain, [9]Hospital General de Alicante, Alicante, Spain, [10]Hospital Clínico San Carlos, Madrid, Spain, [11]Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Spain*

**Background:** Recent studies suggest that baricitinib added to dexamethasone may reduce mortality in hospitalized COVID-19 patients requiring supplemental oxygen

**Methods:** In a multicenter open-label, pragmatic, randomized clinical trial in 25 hospitals in Spain we included symptomatic participants with SARS-CoV-2 detected by PCR or antigenic test, with a creatinine clearance >60 mL/min, > 60 years or younger if they had at least two comorbidities (hypertension, obesity, diabetes, cirrhosis, chronic neurologic disease, active cancer, heart failure, coronary heart disease or COPD). Participants were initially randomized to receive or not tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). At any moment during the trial participants with room air 02 saturation < 95% and at least one increased inflammatory biomarker could be randomized to dexamethasone (D) or dexamethasone plus baricitinib (DB). Primary outcome was 28 days mortality. Secondary outcomes were disease progression (increase of 02 requirements, mechanical ventilation or increase in medical therapy: steroid dose, need for starting tocilizumab)

**Results:** Out of the 355 participants included in the trial 287 (80.8%) were randomized to D (n=142) or DB (n=145), 264 (91.9%) simultaneously with the TDF/FTC randomization and 23 (8.1%) later on. Median age 67 years (IQR 62, 73), male (65.5%), with median 8 days of symptoms (IQR 5-10), 28.6% with ≤ 5 days of symptoms, 100% hospitalized, 31.6% with one and 38.7% with ≥ 2 comorbidities (most common: 35.9% hypertension, 9.4% diabetes, 1.7 % obesity), 14.3% receiving remdesivir and 49.1% TDF/FTC. Endpoints in participants treated with D vs. those treated with DB favored DB without achieving statistical significance: mortality 4.9%/2.1%, disease progression 27.5%/24.8%, mechanical ventilation (invasive or noninvasive) 25.4%/23.4%, days since randomization until discharge (median [IQR]) 7 [5, 12]/7 [5, 13.5], discharge before 28 days 89%/94.2%. By Cox regression Hazard Ratio (95% CI) of 28-day mortality was 0.51 (0.13-2.06) for participants treated with DB. Serious adverse events occurred in 9.9%/9.7% of participants treated with D or DB respectively. Adverse events leading to B discontinuation occurred in 3.45% of participants.

**Conclusion:** In this clinical trial of high-risk patients with COVID-19 all disease outcomes favored baricitinb added to dexamethasone but differences did not reach statistical significance. Overall mortality was unexpectedly low.

Table 1. Patient Enrollment, Disposition and Baseline Characteristics.

| | Aviptadil n (%) | Placebo n (%) | Total n (%) |
|---|---|---|---|
| Screened | -- | -- | 213 |
| Randomized | 136 | 67 | 203 |
| Randomized and Treated | 131 (100) | 65 (100) | 196 (100) |
| Completed Day 28 | 85 (64.9) | 45 (69.2) | 130 (66.3) |
| Died between Day 1 and Day 28 | 41 (31.3) | 18 (27.7) | 59 (30.1) |
| Completed Day 60 | 80 (61.1) | 34 (52.3) | 114 (58.2) |
| Died between Days 29 and 60 | 5 (3.8) | 12 (18.5) | 17 (8.7) |
| | | | |
| Age (years, mean) | 60.1 | 62.7 | |
| Male (percent) | 64.9 | 76.9 | |
| Tertiary Sites | 94 (71.8) | 50 (76.9) | |
| NIAID 3 | 90 (68.7) | 52 (80) | |
| HFNC | 76 (58.0) | 51 (78.5) | |
| On Vent | 38 (29.0) | 11 (16.9) | |

## 464 RECOVERY AND SURVIVAL IN COVID-19 RESPIRATORY FAILURE, WHEN TREATED WITH AVIPTADIL

**Dushyantha Jayaweera**[1], Jihad G. Youssef[2], Richard A. Lee[3], Philip T. Lavin[4], Rainer Lenhardt[5], David J. Park[6], Javier P. Fernandez[7], Melvin L. Morganroth[8], Jonathan C. Javitt[9]

*[1]University of Miami, Miami, FL, USA, [2]Houston Methodist Research Institute, Houston, TX, USA, [3]University of California Irvine, Irvine, CA, USA, [4]Boston Biostatistics Research Foundation, Boston, MA, USA, [5]University of Louisville, Louisville, KY, USA, [6]Providence St Jude Medical Center/St Joseph Heritage Healthcare, Fullerton, CA, USA, [7]Baptist Hospital, Miami, Miami, FL, USA, [8]Oregon Clinic, Portland, OR, USA, [9]NeuroRx, Inc., Wilmington, DE, USA*

**Background:** COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Vasoactive Intestinal Peptide (VIP) blocks replication of the SARS-CoV-2 virus in alveolar type II cells, inhibits cytokine synthesis, prevents cytopathy, and up regulates surfactant production. Synthetic VIP-aviptadil is a novel strategy to treat patients with COVID-19 and respiratory failure.

**Methods:** This was a prospective, multicenter, randomized, placebo-controlled trial with 196 patients, nasal swab PCR+ for COVID-19 receiving intensive care at 10 U.S. hospitals (6 tertiary care and 4 regional hospitals) to determine if intravenous aviptadil is superior to placebo in achieving recovery from respiratory failure and survival at 60 days post treatment. The analysis was by modified intent to treat (ITT) using a pre-specified logistic regression model. The primary pre-specified endpoint was being alive with no respiratory failure at day 60.

**Results:** There were 213 subjects screened, with 203 eligible and 196 randomized and treated. Baseline characteristics were comparable except for worse NIAID severity for aviptadil (Table 1). All subjects were followed up to 60 days. A favorable trend (OR 1.63; P=.14) was seen for the primary endpoint at 60 days with significance achieved after adjusting for hospital setting. Overall, there was 2.0-fold increased odds of survival (95% CI 1.05-3.88; P<.035) for aviptadil at Day 60 controlling for baseline NIAID score. Odds of survival increased to over 4-fold after adjusting for site of care (Tertiary care vs regional hospital, OR 4.35 (95% CI 1.91, 9.90; P<.035). Logistic regression indicated aviptadil treated patients were also significantly more likely to be discharged earlier than placebo-treated patients (p=0.01). The most common adverse events noted were diarrhea (32.8% vs. 1.5%) and hypotension (26% vs.21.5%) for aviptadil vs. placebo. Additional adverse events occurring more frequently in aviptadil treated patients included acute kidney injury (23.7% vs 20%), hyperkalemia (12.2% vs 6.2%), and atrial fibrillation (11.5% vs 4.6%). Multiple organ dysfunction syndrome (6.9% vs 13.8%) and respiratory failure (12.2% vs 13.8%) occurred more commonly in placebo-treated patients.

**Conclusion:** Treatment with aviptadil demonstrates efficacy in improving the likelihood of recovering from respiratory failure, surviving to 60 days, and reducing hospital stay in critically ill patients with respiratory failure caused by COVID-19.

## 465 DO ALL CRITICALLY ILL COVID-19 PATIENTS BENEFIT FROM INTENSIFYING WITH TOCILIZUMAB?

**Cristina Mussini**[1], Alessandro Cozzi-Lepri[2], Jovana Milic[1], Andrea Cossarizza[1], Gianluca Cuomo[3], Adriana Cervo[3], Federica Carli[3], Sara Volpi[1], Giovanni Guaraldi[1]

*[1]University of Modena and Reggio Emilia, Modena, Italy, [2]University College London, London, UK, [3]Azienda Ospedaliera Universitaria Policlinico di Modena, Modena, Italy*

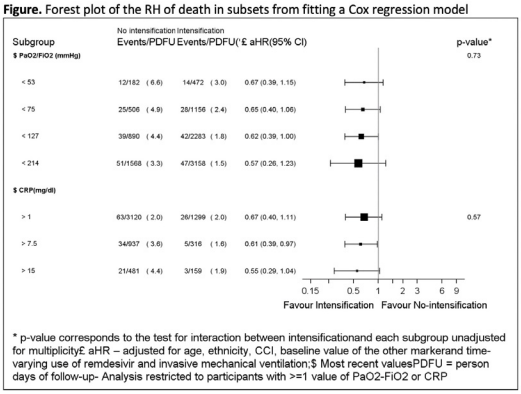
**Background:** Treatment guidelines recommend the use of tocilizumab in patients with a current CRP >7.5 mg/dl. Recent data showed that survival benefit might be greater in those with higher CRP levels. We aimed to estimate the causal effect of intensification with tocilizumab on mortality overall and after stratification for PaO2/FiO2 ratio, CRP levels.

**Methods:** Observational cohort study of patients with severe COVID-19 pneumonia. Primary endpoint was day-28 mortality. Survival analysis was conducted to estimate the conditional and average causal effect of tocilizumab intensification vs. glucocorticoids alone using Kaplan-Meier curves and Cox regression models with a time-varying variable for the intervention. Analysis was controlled for age, ethnicity, duration of symptoms, at hospital admission (baseline, BL) PaO2/FiO2 ratio, CRP (BL and current), Charlson comorbidity index and post-BL use of remdesivir and invasive mechanical ventilation. The hypothesis of the existence of effect measure modification by CRP and PaO2/FiO2 ratio was tested by including an interaction term in the model.

**Results:** 992 patients median age 69 years, 72.9% males, 597 (60.2%) treated with monotherapy and 395 (31.8%), adding tocilizumab upon respiratory deterioration were included. At BL, median CRP was 6.0 mg/dl (IQR 3.0-15.0) and median PaO2/FiO2 ratio was 261 mmHg (200-303). The two groups differed for median values of: CRP (6 vs 7 mg/dL; p<.001)), IL-6, (27.6 vs 175.0 mg/L; p<.001) LDH (525 vs 622 U/L; p<.001), lymphocytes (939 vs 835/mm$_3$; p<.001) and PaO2/FiO2 ratio (276 vs 235 mmHg; p<.001) at BL. In the unadjusted analysis there was no statistically significant difference in mortality between the two groups, but there was strong evidence for an effect of the intensification after controlling for key BL and post-BL confounders, consistent with the estimate in trials (adjusted hazard ratio (aHR)=0.59, 95% CI:0.38-0.90). Although the study was not powered to detect interactions (p>0.57) there was a signal for intensification to have a larger effect in subsets, especially participants with high levels of CRP at intensification (Figure).

**Conclusion:** Our data suggest that intensification with tocilizumab confers reduced survival benefit in those intensifying with a CRP of 0-7.5 mg/dl. It also provides substantial benefit even in patients who are intensified with a CRP>15 mg/dl. Large randomised studies are needed to establish an exact cut-off for clinical use.

**Figure.** Forest plot of the RH of death in subsets from fitting a Cox regression model




* p-value corresponds to the test for interaction between intensificationand each subgroup unadjusted for multiplicity£ aHR – adjusted for age, ethnicity, CCI, baseline value of the other markerand time-varying use of remdesivir and invasive mechanical ventilation;$ Most recent valuesPDFU = person days of follow-up- Analysis restricted to participants with >=1 value of PaO2-FiO2 or CRP

## 466 SARILUMAB PLUS STANDARD OF CARE (SOC) VERSUS SOC FOR SEVERE COVID-19 (ESCAPE STUDY)

New Investigator Scholar

**Ilaria Mastrorosa**[1], Roberta Gagliardini[1], Francesco Vladimiro Segala[2], Annalisa Mondi[1], Patrizia Lorenzini[1], Carlotta Cerva[1], Eleonora Taddei[2], Francesca Bai[3], Maria Maddalena Plazzi[1], Loredana Sarmati[4], Emanuele Nicastri[1], Antonella D'Arminio Monforte[3], Fabrizio Palmieri[1], Antonella Cingolani[2], Andrea Antinori[1]
*[1]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [2]Catholic University of the Sacred Heart, Rome, Italy, [3]Azienda Ospedaliera San Paolo, Milan, Italy, [4]University of Rome Tor Vergata, Rome, Italy*

**Background:** We aimed to evaluate the efficacy of sarilumab, an IL-6 receptor inhibitor, combined with SOC, in patients (pts) affected by severe COVID-19 pneumonia.

**Methods:** Open-label, Phase III, randomized trial assessing clinical efficacy and safety of intravenous sarilumab in pts with severe COVID-19, at 5 clinical centers in Italy. We included hospitalized pts with SARS-CoV-2 infection and pneumonia, in severe or critical condition (excluding mechanically ventilated). Pts were randomized 2:1 to receive sarilumab 400 mg plus SOC (armA) or to continue SOC (armB). The primary endpoint was time to clinical improvement of 2 points on a 7-point category ordinal scale, ranging from 1 (discharged with resumption of normal activities) to 7 (death). Pts were stratified according to baseline disease severity (PaO2/FiO2 ratio < or ≥ 200 mmHg), C reactive protein (CRP < or ≥ 7 mg/dL) and lymphocytes count (< or ≥ 870/mmc). The key secondary endpoint was time to death. Adverse events (AE) were evaluated as safety outcomes. We used chi square test to compare proportions between arms, and Cox regression stratified by clinical center to estimate the hazard risk (HR) of primary endpoint.

**Results:** Of 191 pts screened, 176 were assigned to armA (121) and B (55). A similar proportion of pts were treated with steroids (44 armA vs 26 armB, p=0.170) and remdesivir (22 armA vs 8 armB, p=0.552). 58/121 (48%) pts underwent to a second dose of sarilumab 12 hours after the first dose. At day 30, no significant differences in the primary endpoint were found between the arms (Figure1). After stratifying for inflammatory parameters, the probability of improvement seemed greater in armA than B, for the strata with CRP <7 mg/dL (88% [95% CI 77-96] vs 79% [63-91], HR 1.55 [0.9-2.6]; log-rank p=0.049) and with lymphocytes <870/mmc (90% [79-96]) vs (73% [55-89], HR 1.53 [0.9-2.7]; log-rank p=0.058). Figure2 for interaction tests between strata. There were no significant differences in death probability (armA 5% [2.3-10.9]) and armB 3.6% [0.9-13.8] HR 1.30 [0.41-4.15]; log-rank p=0.79) and in the rates of AE (armA 32% [39/121] and armB 23% [14/55], p=0.195) and serious AE (armA 18% [22/121] and armB 11% [7/55], p=0.244).

**Conclusion:** In our population, efficacy of sarilumab in pts with severe COVID-19 was not confirmed, even if some benefits were shown in those treated at an early stage of the disease with lower inflammatory burden. Further trials are needed for identifying targeted subgroups for maximizing benefit of this treatment.

**Figure 1a-c. Kaplan Meier survival curves estimating the cumulative proportion who experienced the primary endpoint in the entire population (1a) and after stratifying for baseline disease severity ($P_aO_2/FiO_2$ ratio < 200 mmHg [1b] and $P_aO_2/FiO_2$ ratio ≥ 200 mmHg [1c]).** *Cox regression model stratified by clinical center fitted to estimate the hazard risk (HR) of primary endpoint in arm A versus arm B.* ***Primary endpoint:*** *time to clinical improvement of 2 points on a 7-point category ordinal scale.* ***Arm A:*** *sarilumab plus standard of care.* ***Arm B:*** *standard of care.*

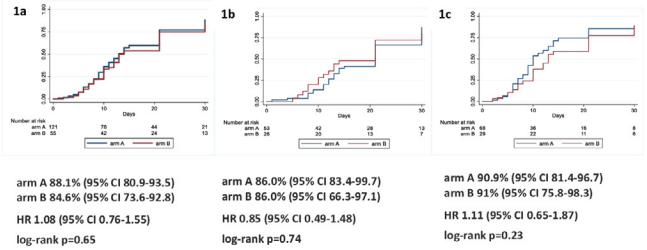
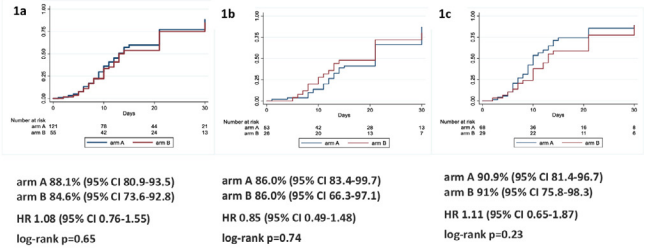



**Figure 1a-c. Kaplan Meier survival curves estimating the cumulative proportion who experienced the primary endpoint in the entire population (1a) and after stratifying for baseline disease severity ($P_aO_2/FiO_2$ ratio < 200 mmHg [1b] and $P_aO_2/FiO_2$ ratio ≥ 200 mmHg [1c]).** *Cox regression model stratified by clinical center fitted to estimate the hazard risk (HR) of primary endpoint in arm A versus arm B.* ***Primary endpoint:*** *time to clinical improvement of 2 points on a 7-point category ordinal scale.* ***Arm A:*** *sarilumab plus standard of care.* ***Arm B:*** *standard of care.*




## 467 CONVALESCENT PLASMA FOR OUTPATIENTS WITH EARLY COVID-19: A RANDOMIZED TRIAL

New Investigator Scholar

**Arvind Gharbharan**[1], Pere Millat-Martinez[2], Andrea Alemany[3], Casper Rokx[1], Corine H. Geurts van Kessel[1], Grigorios Papageourgiou[1], Carlijn Jordans[1], Marc Corbacho-Monné[3], Quique Bassat[2], Bonaventura Clotet[3], Bàrbara Baro[2], Jaap Jan Zwaginga[4], Oriol Mitjà[3], Bart J. Rijnders[1]
*[1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]ISGlobal, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain, [3]Fight AIDS and Infectious Diseases Foundation, Badalona, Spain, [4]Leiden University Medical Center, Leiden, Netherlands*

**Background:** Trials on convalescent plasma (CP) for hospitalized patients with COVID-19 have not demonstrated clear benefits. However, data on outpatients with early symptoms are limited. We studied if treatment with CP reduces disease burden of outpatients treated in the first 7 days of symptoms.

**Methods:** Two double blind randomized trials (NCT04621123, NCT04589949) were merged. Pooling of data started when <20% of their predefined sample size had been recruited. A Bayesian adaptive individual patient data meta-analysis was implemented. Analyses were done with Bayesian proportional odds and logistic models, where odds ratios(OR)<1.0 indicate a favorable outcome for CP. A DSMB monitored the accumulating data for efficacy. Patients aged ≥50, diagnosed with COVID-19 and symptomatic for ≤7days were eligible for participation. The intervention was one unit (200-300mL) of CP with a predefined minimum level of antibodies. The two primary endpoints were (a) a 5-point disease severity scale (fully recovered by day 7 or not, hospital or ICU admission and death) and (b) a composite of hospitalization or death. Secondary endpoints were efficacy in patients with ≤5days of symptoms and time to full symptom resolution.

**Results:** Of 797 patients included, 390 received CP and 392 placebo. They had a median age of 58, 1 comorbidity, symptoms for 5 days and 93% tested negative for SARS-CoV-2 S-protein IgG antibodies. 74 patients were hospitalized, 6 required mechanical ventilation and 3 died. The OR of CP for an improved disease severity scale was 0.936 (credible interval (CI) 0.667-1.311). The OR for hospitalization or death was 0.919 (CI 0.592-1.416). The effect of CP on hospital admission or death was largest in patients with ≤5days of symptoms (OR 0.658, 95% CI 0.394-1.085). CP did not decrease the time to full symptom resolution (p=0.62).
**Conclusion:** Treatment with CP of outpatients in the first 7 days of symptoms did not improve outcome of COVID-19. The possible beneficial effect in patients with ≤5days of symptoms requires further study.

**Table.** Distribution of the outcome of the patients in the 28 days after inclusion across the 5-points disease severity scale.

| Worst Disease Severity Score | Total (n = 782) | CP* (n = 390) | Control (n = 392) |
|---|---|---|---|
| Fully recovered on day 7 after inclusion – no. (%) | 143 (18.3%) | 74 (19.0%) | 69 (17.6%) |
| Continued symptoms on day 7 after inclusion– no. (%)‡ | 565 (72.3%) | 282 (72.3%) | 283 (72.2%) |
| Admitted to hospital but no invasive ventilation needed – no. (%) | 65 (8.3%) | 31 (7.9%) | 34 (8.7%) |
| Admitted to hospital and invasive ventilation needed – no. (%) | 6 (0.8%) | 2 (0.5%) | 4 (1.0%) |
| Death – no. (%) | 3 (0.4%) | 1 (0.3%) | 2 (0.5%) |

*Convalescent plasma

‡Continued symptoms attributable to COVID-19

## 468 ENPATORAN SAFETY AND EFFICACY IN COVID-19 PNEUMONIA: ANEMONE TRIAL

Late Breaking

**John McKinnnon**[1], Joel Santiaguel[2], Claudia Murta[3], Dongzi Yu[4], Mukhy Khursheed[5], Flavie Moreau[4], Sanjeev Roy[6], Amy Kao[4]
*[1]Henry Ford Hospital, Detroit, MI, USA, [2]Quirino Memorial Medical Center, Quezon City, Philippines, [3]Santa Casa de Misericórdia, Belo Horizonte, Brazil, [4]EMD Serono, Billerica, MA, [5]Merck Serono Ltd, Feltham, UK, [6]Ares Trading SA, Eysins, Switzerland*

**Background:** Enpatoran, a selective and potent toll-like receptor 7 and 8 (TLR7/8) inhibitor, is in development for treating autoimmune diseases. Enpatoran may prevent hyperinflammation and cytokine storm in COVID-19 by targeting pro-inflammatory pathways induced by SARS-CoV-2.
**Methods:** The ANEMONE study, a phase II, randomized, double-blind, placebo-controlled trial conducted in the US, the Philippines, and Brazil, assessed the safety and efficacy of enpatoran in COVID-19 pneumonia (NCT04448756). Eligible hospitalized patients were aged 18–75 years, with a WHO 9-point scale score of 4, confirmed COVID-19 pneumonia, SpO2 <94%, PaO2/FiO2 ≥150 (FiO2 max 0.4) and not on mechanical ventilation. Key exclusion criteria were active/unstable cardiovascular disease, history of uncontrolled illness and SARS-CoV-2 vaccination. Randomized patients (N=149) received placebo (PBO; n=49), enpatoran 50 mg twice daily (BID; n=54) or 100 mg BID (n=46) for 14 days, with monitoring up to Day 28 and safety follow-up to Day 60. Primary outcomes were safety and time to recovery (WHO 9-point scale ≤3). Clinical deterioration (time to clinical status >4, WHO 9-point scale) was a secondary outcome.
**Results:** 88% of patients completed treatment (66% male, median age 50 years); 50% had ≥1 comorbidity (including 40% hypertension, 24% diabetes). Treatment-emergent adverse events (TEAEs) were reported by 59% of patients; 11% reported treatment-related TEAEs (Table). Serious TEAEs were higher with PBO (18%) than enpatoran (6%). Three non-treatment-related deaths occurred. Gastrointestinal disorders were most common (PBO 8%; 50 mg BID 28%; 100 mg BID 9%). Infections and infestations were reported by 18% (PBO), 17% (50 mg BID) and 4% (100 mg BID); COVID-19 worsening (PBO 8%; 50 mg BID 9%) and bacterial sepsis (PBO 4%) were most common. Headache and dizziness were only reported with enpatoran (<3% across groups). Psychiatric disorders were higher with PBO (14%) than enpatoran (50 mg BID 7%; 100 mg BID 4%). There was no dose effect on TEAEs. Median [95% CI] time to recovery from Day 1 through Day 28 was 3.4 [2.7, 4.9] (PBO), 3.7 [2.6, 4.0] (50 mg BID) and 3.9 [2.0, 4.8] (100 mg BID) days. A positive signal in time to clinical deterioration from Day 1 through Day 28 was observed; hazard ratios [95% CI] for enpatoran versus PBO were 0.39 [0.13, 1.15] (50 mg BID) and 0.30 [0.08, 1.08] (100 mg BID).
**Conclusion:** Enpatoran was considered safe and well tolerated in hospitalized patients with acute COVID-19 pneumonia.

**Table. Overview of adverse events reported during the trial**

| Number (%) subjects with any | Placebo (n=49) | 50 mg BID (n=54) | 100 mg BID (n=46) | Total (N=149) |
|---|---|---|---|---|
| TEAE | 28 (57) | 34 (63) | 26 (57) | 88 (59) |
| Treatment-related TEAE | 4 (8) | 8 (15) | 5 (11) | 17 (11) |
| Serious TEAE | 9 (18) | 5 (9) | 1 (2) | 15 (10) |
| Serious treatment-related TEAE | 1 (2) | 0 | 0 | 1 (1) |
| Treatment-related TEAE grade ≥3 | 1 (2) | 1 (2) | 0 | 2 (1) |
| Treatment-related TEAE grade ≥4 | 0 | 0 | 0 | 0 |
| TEAE leading to death | 2 (4)* | 1 (2)** | 0 | 3 (2) |
| Treatment-related TEAE leading to death | 0 | 0 | 0 | 0 |
| TEAE leading to treatment discontinuation | 4 (8) | 4 (7) | 1 (2) | 9 (6) |
| Treatment-related TEAE leading to discontinuation | 0 | 3 (6) | 1 (2) | 4 (3) |

*Due to sepsis; **Due to COVID-19 worsening.

## 469 IMPACT OF TENOFOVIR ON SARS-CoV-2 INFECTION AMONG PEOPLE LIVING WITH HIV

Late Breaking

**Daniel Kwakye Nomah**[1], Juliana Reyes-Urueña[1], Yesika Diaz[1], Sergio Moreno Fornés[1], Jordi Aceiton[1], Andreu Bruguera[1], Rosa M. Vivanco-Hidalgo[2], Jordi Casabona[1], Pere Domingo[3], Jordi Navarro[4], Arkaitz Imaz[5], Elisabet Deig[6], Gemma Navarro[7], Josep M Llibre[8], Jose M. Miro[9]
*[1]Centre d'Estudis Epidemiològics Sobre les ITS i Sida de Catalunya, Barcelona, Spain, [2]Aalborg University Hospital, Aalborg, Denmark, [3]Hospital de Sant Pau, Barcelona, Spain, [4]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [5]Bellvitge University Hospital, Barcelona, Spain, [6]Hospital General de Granollers, Granollers, Spain, Granollers, Spain, [7]Corporació Sanitària i Universitària Parc Taulí, Barcelona, Spain, [8]Hospital Germans Trias i Pujol, Barcelona, Spain, [9]Hospital Clinic of Barcelona, Barcelona, Spain*

**Background:** The impact of some antiretrovirals against SARS-CoV-2 infection and disease severity is conflicting. We evaluated the effect of tenofovir alafenamide/emtricitabine (TAF/FTC) and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) against SARS-CoV-2 infection and associated clinical outcomes among people living with (PLWH).
**Methods:** We conducted a propensity score-matched analysis leveraging data from the PISCIS cohort of PLWH in Catalonia (Spain). We matched for TAF/FTC versus ABC/3TC in a ratio of 1:1, and 1:3 for TDF/FTC versus ABC/3TC, and TDF/FTC versus TAF/FTC. We used logistic regression to assess the association between tenofovir-based ART and SARS-CoV-2 diagnosis and associated hospitalisation.
**Results:** In our entire cohort [median age: 46·1 years, 82·3% males], 7550 PLWH were being treated with TAF/FTC, 1020 receiving TDF/FTC, and 4135 receiving ABC/3TC. After propensity score-matching, SARS-CoV-2 diagnosis rates were the same in TAF/FTC versus ABC/3TC recipients (12·2% vs 12·2%, P=1·00); lower among TDF/FTC versus ABC/3TC recipients (9.7% vs 12.4%, P=0·05) with borderline significance; and lower among TDF/FTC versus TAF/FTC recipients (9·7% vs 12·6%, P=0·03). In well-adjusted logistic regression models, TAF/FTC was not associated with reduced SARS-CoV-2 diagnosis (adjusted odds ratio [aOR] 0·97; 95% confidence interval [CI], 0·83 - 1·12) or associated hospitalisation (aOR 0·95; 95% CI, 0·62 - 1·45). TDF/FTC compared to ABC/3TC, was not associated with reduced SARS-CoV-2 diagnosis (aOR 0·81; 95% CI, 0·61 - 1·07) or hospitalisation (aOR 0·49; 95% CI, 0·14 - 1·27). TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aOR 0·81; 95% CI, 0·61 - 1·07) or associated hospitalisation (aOR 0·47; 95% CI, 0·14 - 1·22) compared to TAF/FTC.
**Conclusion:** TAF/FTC or TDF/FTC were not associated with reduced SARS-CoV-2 diagnosis rates or associated hospitalisations among PLWH. TDF/FTC users had baseline characteristics intrinsically associated with more benign SARS-CoV-2 infection outcomes. Tenofovir exposure or not should not modify the preventive or therapeutic SARS-CoV-2 infection management.

## 470 PBI-0451 AN ORALLY ADMINISTERED 3CL PROTEASE INHIBITOR OF SARS-CoV-2 FOR COVID-19

Late Breaking

**Brian P. Kearney**[1], Andrew Plummer[1], Grushenka Wolfgang[1], David Turnquist[1], Mark R. Marshall[2], Mark Denison[3], Christian Schwabe[2], Uri Lopatin[1], Lee Arnold[1]
*[1]Pardes Biosciences, Carlsbad, CA, USA, [2]NZCR, Auckland, New Zealand, [3]Vanderbilt University, Nashville, TN, USA*

**Background:** The 3CL protease (3CLpro) of coronaviruses (CoV) is responsible for essential & early steps of viral replication. Early treatment of SARS-CoV2 infection with a 3CLpro inhibitor has shown to substantially reduce the rate of hospitalization & death from COVID-19. There is a need for a protease inhibitor

that can be used as a stand-alone agent to treat and prevent SARS-CoV-2 infection globally, in the setting of remote testing & healthcare delivery, and as unsupervised outpatient use by a significant number of people who take other medications.

**Methods:** PBI-0451 was assessed in cultures of inducible pluripotent stem cell-derived alveolar type II (iPS-AT2) cells, in nonclinical PK and toxicity studies, and an ongoing randomized, double-blind first-in-human (FIH) study evaluating the tolerability, safety, and PK of single and multiple doses administered as an oral suspension to healthy adult subjects. The effect of food and the potential for a drug-drug interaction (DDI) with ritonavir were also explored.

**Results:** PBI-0451 potently inhibited SARS-CoV-2 replication in iPS-AT2 cells with multi-log reductions in viral titer and mean (SD) $IC_{50}$ & $EC_{90}$ values of 32 (25) & 106 (90) nM, respectively. No clinically relevant adverse effects of PBI-0451 were observed in 14-day GLP toxicity studies in mice and dogs, including on the cardiovascular, CNS, or respiratory systems. PBI-0451 was not genotoxic in Ames and micronucleus tests. In the ongoing FIH study to date, study treatments were generally well tolerated with no study drug or study discontinuations. No Grade 2, 3, 4, or severe adverse events were reported. Preliminary single-dose concentration-time profile of PBI-0451 following administration with food demonstrated a 2-compartment PK profile with a median terminal elimination $t_{1/2}$ ranging from 11-14 hours. PBI-0451 demonstrated good oral bioavailability and a linear increase in exposure over a 10-fold dose range when administered with food, achieving concentrations >1-, 3- & 10-fold the plasma protein binding-adjusted $EC_{90}$ value (374 ng/mL) against SARS-CoV-2 at doses of 100, 300 & 1050 mg, respectively. The PK of PBI-0451 was unaffected by coadministration with ritonavir.

**Conclusion:** PBI-0451 has shown favorable nonclinical properties and early clinical safety & PK that supports its continued evaluation as a stand-alone agent. Ongoing multiple-dose evaluation will further elucidate its clinical profile and inform the dose & dosing regimen selection for potential Phase II/III studies.

## 471 MOLNUPIRAVIR INCREASES RANDOM SARS-CoV-2 RNA ERRORS WITHOUT SELECTION FOR RESISTANCE

Late Breaking

**Arthur Fridman**[1], Nicholas J. Murgolo[1], Andy Liaw[1], Ying Zhang[1], Shunbing Zhao[1], Hong Wan[1], Alison Pedley[1], Min Xu[1], Daria Hazuda[1], Jay A. Grobler[1], Julie M. Strizki[1]

*[1]Merck & Co., Inc., Kenilworth, NJ, USA*

**Background:** Molnupiravir (MOV), the orally administered prodrug of the antiviral ribonucleoside analogue, N-hydroxycytidine (NHC) has received emergency use authorization for treatment of COVID-19. NHC inhibits viral replication by introduction of random transition errors across the viral genome, resulting in non-infectious virus. In the Phase II/III (MOVe-OUT) study, non-hospitalized participants received MOV or placebo (PBO) for 5 days and followed to Day 29. Viral RNA was sequenced to determine the rate, distribution and type of viral errors observed.

**Methods:** SARS-CoV-2 RNA isolated from nasopharyngeal swabs was quantified by RT-PCR followed by complete genome NGS using the Ion AmpliSeq SARS-CoV-2 Research panel and Ion Torrent sequencing. To distinguish between nucleotide errors resulting from the mechanism of action of MOV and those potentially associated with reduced susceptibility to NHC, two different analyses were used. To measure impact of MOV on accumulation of low-frequency errors in the viral quasispecies, nucleotide variants were identified using VarScan 2.4 mutation caller with 0.4% minimum variant allele frequency cut-off. Resistance-associated changes were identified as amino acid substitutions occurring in D3 or D5 samples from ≥2 participants with a frequency of ≥5% of NGS reads. Phenotypic analysis of selected amino acid substitutions was performed using a replicon model.

**Results:** NGS results showed a relationship between the number of random errors across the viral genome with increasing MOV dose. By Day 5 the mean number of viral genome errors were 21, 83, 129 and 223 in the PBO, 200, 400 and 800 mg groups, respectively. Among the sequence changes observed, the majority were transitions errors, consistent with MOV's mechanism of action. After MOV treatment, few treatment-emergent amino acid substitutions were identified in the viral replicase genes. These included nsp12 (T731I) and nsp14 (A220S/T/V, V466I, S503L/P); none associated with loss of susceptibility to MOV. Changes in spike protein in both PBO and MOV groups were at sites previously described in circulating variants.

**Conclusion:** Consistent with the mechanism of action, MOV treatment resulted in a dose-dependent increase in transition errors across the SARS-CoV-2 genome. No resistance-associated mutations were identified in the viral replicase and no evidence that MOV treatment selected for unique mutations in spike protein not previously observed in circulating variants.

## 472 WITHDRAWN

## 473 GUNNERA PERPENSA ELLAGITANNINS SYNERGISTICALLY INHIBIT MULTIPLE SARS-CoV-2 VARIANTS

**Ian Tietjen**[1], Luke Invernizzi[2], Phanankosi Moyo[2], Joel Cassel[1], Emery T. Register[1], Frederick Keeney[1], Joseph M. Salvino[1], Freddie J. Isaacs[3], Vinesh Maharaj[2], Luis J. Montaner[1]

*[1]Wistar Institute, Philadelphia, PA, USA, [2]University of Pretoria, Pretoria, South Africa, [3]Pure Herbal Medicine, Uitenhage, South Africa*

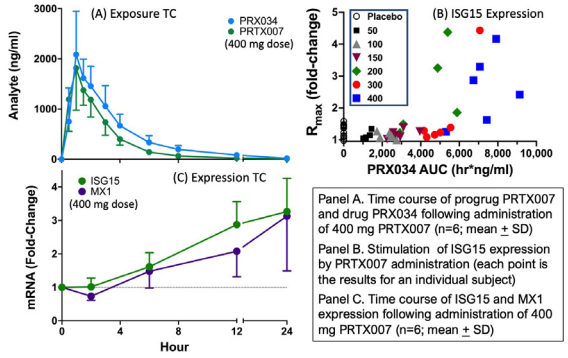
**Background:** Antivirals are urgently needed to supplement SARS-CoV-2 vaccines and target SARS-CoV-2 variants of concern, particularly in resource-limited regions. Active derivatives from the medicinal plant Gunnera perpensa, already in use as a general antiviral in humans by traditional health practitioners in the Eastern Cape Province of South Africa, warrant further evaluation against SARS-CoV-2.
**Methods:** Active constituents of Gunnera perpensa were identified using hyphenated analytical techniques and for ability to inhibit binding of recombinant SARS-CoV-2 spike with host ACE2 protein as assessed by AlphaScreen. Inhibition was tested against parental (USA-WA1/2020), beta (B.1.351), and delta (B.1.617.2) spike proteins using AlphaScreen and spike-expressing VSVΔG-GFP pseudoviruses. Infection of Vero cells was monitored by high-content imaging of GFP or nucleocapsid-positive Vero-E6 cells in pseudovirus and virus assays, respectively, at 2 days post-infection (dpi). Viral cytopathic effect (CPE) ± GC-376 or remdesivir was also monitored using resazurin viability dye at 4 dpi. All assays were described previously (PMID: 34543092). Synergism was assessed by the Bliss Independence model, and group differences were analyzed by two-sided, paired t-test.
**Results:** Crude extracts from the leaves of Gunnera perpensa were confirmed to inhibit parental spike/ACE2 interactions with an $IC_{50}$ of 37 ± 23 ng/mL. Bioassay-guided fractionation identified two ellagitannins, punicalin and punicalagin, which inhibited parental, beta, and delta spike/ACE2 binding with $IC_{50}$s of 2.7 ± 0.6 – 5.8 ± 4.8 and 6.0 ± 4.5 – 19 ± 23 nM, respectively. Both compounds inhibited all spike variants in pseudovirus at low to mid micromolar concentrations (see Table). Notably, in CPE-based viral assays, a 1:1 molar mixture of punicalin and punicalagin significantly enhanced antiviral activity ($EC_{50}$ = 2.9 µM vs. 11.6 and 46.8 µM for single compounds, $p < 0.05$), on par with activities of preclinical candidate GC-376 (1.3 µM) and remdesivir (2.8 µM; see Table). When combined in a 1:1 molar mixture, punicalin further significantly enhanced activity of GC-376 ($EC_{50}$ = 0.6 µM, $p < 0.05$) and remdesivir ($EC_{50}$ = 1.1 µM, $p < 0.05$).
**Conclusion:** Punicalin and punicalagin inhibit entry and replication of SARS-CoV-2 variants in vitro and synergize when applied in combination and/or with GC-376 or remdesivir. Ellagitannins and medicinal plant extracts are promising new leads for SARS-CoV-2 antivirals in resource-limited regions.

| | Assay | Compound | WA1/2020 | Beta | Delta |
|---|---|---|---|---|---|
| $EC_{50}$ (µM) | Pseudovirus (BHK21/WI-2 cells) | Punicalin | 6.7 | 7.1 | 11.8 |
| | | Punicalagin | 36.4 | 39.8 | 41.5 |
| | Infectious virus (Vero E6 cells; 48 h) | Punicalin | 0.8 | 1.2 | 0.9 |
| | | Punicalagin | 11.1 | 4.9 | 2.7 |
| | Infectious virus (Vero E6 cells; 96 hours) | Punicalin | 11.6 | - | - |
| | | Punicalagin | 46.8 | - | - |
| | | Punicalin + Punicalagin (1:1) | 2.9 | - | - |
| | | GC-376 | 1.3 | - | - |
| | | punicalin + GC-376 (1:1) | 0.6 | - | - |
| | | Remdesivir | 2.8 | - | - |
| | | punicalin + remdesivir (1:1) | 1.1 | - | - |

## 474 INTERIM ANALYSIS OF A PHASE I STUDY OF PRTX007: SAFETY, PK, AND PD RESPONSE

**Charlotte R. Lemech**[1], Curtis L. Scribner[2], Richard Daniels[3], James R. Appleman[3]
*[1]Scientia Clinical Research, LTD, Randwick, Australia, [2]Independent Consultant, Oakland, CA, USA, [3]Primmune Therapeutics, Carlsbad, CA, USA*

**Background:** PRTX007 is a prodrug of PRX034, a novel TLR7 agonist, for treatment of respiratory viral diseases including SARS-CoV-2. PRX034 activates plasmacytoid dendritic cells to preferentially synthesize poly sub-type interferons while minimizing NFκB-mediated proinflammatory factors. Pre-clinical studies have demonstrated decoupling of these two normally linked processes in human PBMCs in vitro and in cynomolgus monkeys in vivo. Antiviral activity is preserved, as demonstrated by inhibition of cytopathicity and viral replication in RNA viruses by conditioned media from PRX034-treated PBMCs. Efficacy and safety have been demonstrated in a murine model of RSV infection. An interim analysis of the first-in-human study in healthy volunteers is presented here.
**Methods:** Phase I, single-center, prospective, randomized, double-blind study of 8 single-ascending dose (SAD) cohorts and 4 multiple-ascending dose (MAD) cohorts of PRTX007 administered orally to healthy adult subjects. Primary objective was safety and tolerability. Secondary objectives were to assess pharmacokinetics (PK) and pharmacodynamics (PD). This interim analysis focuses on the SAD portion of the study over 8 dose levels from 50-600mg. Safety through all SAD cohorts, PK up to the 500 mg cohort, PD up to the 400 mg cohort are presented. The MAD cohort safety data from 3 of 4 planned cohorts are also presented.
**Results:** Treatment-related adverse events (AEs) include mild to moderate headache. Severity or frequency is not dose related, is of short duration and is not associated with systemic symptoms. One participant in the 400 mg cohort had asymptomatic mild sinus tachycardia, attributed to PRTX007. Two subjects in the second MAD cohort at 300 mg had mild increases in ALT that rapidly resolved after treatment. PK analysis demonstrated efficient conversion of PRTX007 to PRX034 with systemic exposure to drug and prodrug increasing proportionally with dose. Duration of systemic exposure to PRX034 at pharmacologically active levels is consistent with activation of innate immune response without counter-regulation (Panel A). Exposure-dependent PD response measured by induction of interferon stimulated genes in the blood is observed at drug AUC > 4,300 hr*ng/ml (Panel B); duration of induction >24 hours (Panel C).
**Conclusion:** Interim analysis of PRTX007 demonstrates a favorable safety profile with dose-dependent systemic exposure and demonstrated activation of innate immune response.




## 475 CETYLPYRIDINIUM CHLORIDE MOUTHWASHES TO REDUCE THE SHEDDING OF VIABLE SARS-CoV-2

New Investigator Scholar

**Jordana Muñoz-Basagoiti**[1], Andrea Alemany[2], Daniel Perez-Zsolt[1], Dan Ouchi[2], Dalia Raïch-Regué[1], Benjamin Trinité[1], Edwards Pradenas[1], Julià Blanco[1], Ruben León[3], Vanessa Blanc[3], Joan Gispert[3], Bonaventura Clotet[1], Oriol Mitjà[2], Nuria Izquierdo-Useros[1]
*[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Hospital Germans Trias i Pujol, Barcelona, Spain, [3]Dentaid Research Center, Cerdanyola del Vallès, Spain*

**Background:** SARS-CoV-2 is spread via airborne transmission. Mouthwashes containing virucidal compounds can help reduce viral spread. Here we show that cetylpyridinium chloride (CPC), a quaternary ammonium present in many oral mouthwashes, reduces SARS-CoV-2 infectivity by disrupting viral membranes both in vitro and in vivo.
**Methods:** We tested the capacity of CPC-containing mouthwashes to inhibit SARS-CoV-2 entry into target cells by using a luciferase-based assay with a reporter lentivirus pseudotyped with the SARS-CoV-2 spike protein. The replication-competent SARS-CoV-2 B.1.1.7 and D614G variants were also assayed. Viral envelope disruption by CPC's virucidal effect was measured by dynamic light-scattering analyses (DSL). We confirmed these results by modifying an ELISA that detects the SARS-CoV-2 nucleocapsid (NC), which was used in the absence of its own lysis buffer. The effect of CPC in the saliva of individuals with CoVID-19 was assessed in a double-blind, placebo-controlled, randomized clinical trial. SARS-CoV-2 positive patients were randomized to gargle either water or 0.07% CPC mouthwash. The study outcomes were the SARS-CoV-2 $log_{10}$ viral RNA load by RT-PCR and the NC protein levels by ELISA, both in saliva at 1h and 3h post-intervention.
**Results:** CPC-containing mouthwashes inhibited SARS-CoV-2 viral fusion in vitro in a dose-dependent manner and decreased more than a 1000 times the viral TCID50 in target cells, regardless of the variant tested. The ELISA and the DSL analyses pointed to the effective disruption of the integrity of viral membranes after treatment with CPC. The clinical study performed with 105 patients showed no significant differences in viral RNA load at 1h and 3h post-

treatment in saliva between placebo and CPC-treated groups. However, the levels of SARS-CoV-2 NC protein of lysed viruses were significantly higher in the CPC group at 1h and 3h post-intervention.

**Conclusion:** CPC decreased more than a 1000 times the infectivity of SARS-CoV-2 in vitro and was effective against different SARS-CoV-2 variants. In CoVID-19 patients, the use of a 0.07% CPC mouthwash correlated with a statistically significant increase of NC protein levels in saliva, indicating enhanced disruption of viral particles. CPC-containing mouth rinses can represent a cost-effective measure to reduce SARS-CoV-2 infectivity in saliva, aiding to reduce viral transmission from infected individuals regardless of the variants they are infected with.

## 476 A NOVEL CLASS OF ANTIVIRAL COMPOUNDS WITH POTENT ACTIVITY AGAINST SARS-CoV-2

**David E. Gordon**[1], Eugene Stavtsev[2], Anatolii Demchenko[2]
*[1]Emory University, Atlanta, GA, USA, [2]Viradem, Inc., Cheyenne, WY, USA*

**Background:** The SARS-CoV-2 pandemic has sickened over 245 million people, and has killed more than 5 million worldwide. Recent data proves that vaccinations are highly effective in preventing Covid-19 disease, however antigenic drift and other functional mutations in the virus genome reduce the efficacy of vaccines, indicating that the development of antiviral treatments remain a crucial priority. We report potent antiviral activity against SARS-CoV-2 for a promising, novel class of nitrogen-based heterocyclic compounds.

**Methods:** 232 compounds based on the same class of nitrogen-based hetereocyclic molecules were synthesized to final purity of greater than 99%. This library was screened for antiviral phenotypes in a cytopathic effect (CPE) assay using VeroE6 cells and the SARS-CoV-2 WA1 isolate. Based on the results of the WA1 CPE screen, 47 lead candidates were structurally analyzed, and this information was utilized to design 56 additional compounds. A second antiviral CPE-based screen was performed using these 103 candidates in VeroE6 cells with the SARS-CoV-2 delta variant. Antiviral assays studying SARS-CoV-1 (Urbani) and MERS-CoV were performed in Vero 76 cells utilizing a Neutral Red cytopathic effect assay.

**Results:** Within the same class of structurally related small molecules, we tested an initial set of 232 compounds using a CPE-based assay with VeroE6 cells and the USA/WA1 SARS-CoV-2 isolate. Of the compounds tested, 124 demonstrated potency 10 to 540-times higher than a Remdesivir control tested in parallel. Importantly, we observed no detectable toxicity for the vast majority of these compounds when tested up to a concentration of 30 µM. The lead candidate in this screen displayed an $IC_{50}$ of 0.02 µM and a selectivity index of >1,500. Based on structural analysis of an initial 47 lead candidates, we synthesized 56 new molecules, and tested all 103 in a CPE-based assay using the delta variant, also observing efficacy against this variant of concern. Examples of this same class of compounds also display antiviral activity against SARS-CoV-1 (Urbani) and MERS-CoV in cell-based assays.

**Conclusion:** We have identified a novel class of antiviral compounds with potent activity against SARS-CoV-2. High potency against both the early WA1 isolate and the more recent delta variant, as well as efficacy against SARS-CoV-1 and MERS-CoV, suggest that this class of antiviral compounds has pan-Coronavirus antiviral activity.

## 477 DESIGN OF NOVEL AND HIGHLY SELECTIVE SARS-CoV-2 MAIN PROTEASE INHIBITORS

**Joseph M. Salvino**[1], Ian Tietjen[1], Adi Narayana Reddy R. Poli[1], Joel Cassel[1], Troy E. Messick[1], Emery T. Register[1], Frederick Keeney[1], Luis J. Montaner[1]
*[1]Wistar Institute, Philadelphia, PA, USA*

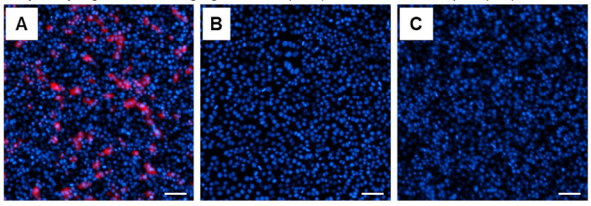
**Background:** SARS-CoV-2 has caused a global pandemic, yet despite vaccine availability, it continues to inflict morbidity and mortality worldwide. The viral main protease (Mpro) is highly conserved across multiple coronaviruses and has a unique viral substrate specificity. Thus, highly selective Mpro inhibitors are expected to be safe, effective, and elude drug resistance for future coronaviruses.

**Methods:** We used a conformationally restricted peptidomimetic to mimic the bioactive conformation of the Mpro-substrate complex to identify potent, selective Mpro inhibitors. We evaluated protease inhibition in biochemical assays, and cellular efficacy in Vero-E6 cells challenged with live virus representing parental (USA-WA1/2020), beta (B.1.351), and delta (B.1.617.2) variants by monitoring infection at day 2 post-infection measuring nucleocapsid-positive cells by high content imaging, and cytopathic effect (CPE) at day 4 post-infection using resazurin viability dye. Results were compared to reference compounds. Group differences were analyzed by two-sided, paired t-test.

**Results:** AP-8-013 required a 2-hour incubation to achieve maximal dose-dependent Mpro inhibition with an $IC_{50} = 230 \pm 18$ nM, reflecting its highly constrained conformation, compared to the more flexible Cpd 22 (AP-8-001; $IC_{50} = 11 \pm 0.7$ nM) or GC-376 ($IC_{50} = 18 \pm 1.5$ µM). Importantly, AP-8-013 showed exquisite selectivity for Mpro with no inhibition at key mammalian cysteine proteases, cathepsin B and L, or the serine protease thrombin, while Cpd 22 (Cat B $IC_{50} = 24 \pm 7.5$ nM, Cat L $IC_{50} = 1.8 \pm 0.3$ nM) or GC-376 (Cat B $IC_{50} = 37 \pm 1.5$ nM, Cat L $IC_{50} = < 1$ nM) showed poor selectivity towards mammalian cysteine proteases. AP-8-013 was active in CPE cell-based assays with comparable potency to reference compounds, with $EC_{50} = 4.7$ µM compared to Cmp 22 ($EC_{50} = 1.4$ µM) or GC-376 ($EC_{50} = 1.1$ µM). Using intact SARS-CoV-2 infection-based assays, AP-8-013 significantly inhibited parental virus as well as beta and delta VOC ($EC_{50}$s = 2.7, 2.5, and 6.0 µM, respectively). Finally, a 3:1 molar mixture of AP-8-013 and remdesivir significantly enhanced antiviral activity in CPE assays ($EC_{50} = 1.3$ µM; $p < 0.05$) when compared against either compound alone ($EC_{50}$s = 4.7 and 3.3 µM, respectively).

**Conclusion:** We have identified a novel drug-like Mpro inhibitor lead series which is highly selective over cysteine and serine proteases that can inhibit multiple SARS-CoV-2 VOC and increase the antiviral activity of remdesivir.

**Figure. Infection assay + USA-WA1/2020.** Treatment comparison of **(A)** 0.1% DMSO; **(B)** GC-376 (3 µM); or **(C)** AP-8-013 (3 µM) after 48-hour infection in Vero-E6 cells. Analysis by high content imaging; Hoechst (blue) and viral nucleocapsid (red).




## 478 EFFECT OF ASTODRIMER SODIUM AGAINST SARS-CoV-2 VARIANTS (A, B, Γ, Δ, K) IN VITRO

**Philippe Gallay**[1], Carolyn Luscombe[2], Winston Stauffer[1], Michael D. Bobardt[1], Graham Heery[2], Alex Castellarnau[2], Aynaz Seta[2], Jeremy R. Paull[2]
*[1]The Scripps Research Institute, La Jolla, CA, USA, [2]Starpharma Pty Ltd, Abbotsford, Australia*

**Background:** The dominance of SARS-CoV-2 Variants of Concern (VOC) and Interest (VOI) has challenged the efficacy of public health strategies to control the current pandemic. Astodrimer sodium is a broad-spectrum antiviral dendrimer that has been formulated as a topical nasal spray to help reduce exposure to infectious viral load in the nasal cavity. Astodrimer sodium showed antiviral and virucidal activity against early pandemic isolates of SARS-CoV-2 in vitro and after nasal administration in vivo. The current studies assessed the spectrum of activity of astodrimer sodium against emerging variants of SARS-CoV-2 and other pandemic viruses.

**Methods:** Assays utilized hACE2+ and hTMPRSS2+ HEK-293T cells, Calu-3 and Vero E6 cells. Time of addition studies involved adding astodrimer sodium 1 hour prior to, at the time of, or 1-hour post-infection. Coronavirus spike receptor binding domain (RBD) or S1 binding studies were analysed by ELISA or confocal microscopy. Virucidal studies involved exposing 105 SARS-CoV-2 PFU to 10mg/mL astodrimer sodium for 0.5, 1, 5, 15 and 30 mins.

**Results:** Astodrimer sodium demonstrated potent antiviral and virucidal activity against SARS-CoV-2 VOC α, β, δ and γ, and VOI κ in Vero E6 and Calu-3 cells. Astodrimer sodium reduced infectious viral load of all variants by >99.9% vs virus control. The pan-SARS-CoV-2 activity of astodrimer sodium occurred despite multiple mutations and deletions in the viral spike protein of each variant. The attachment of SARS-CoV-2 early pandemic virus isolates, Wuhan-Hu-1 and USA-WA-1/2020, and SARS-CoV-1 Spike binding to ACE2, as well as attachment of Middle Eastern respiratory syndrome (MERS) coronavirus spike protein to its cellular receptor, was inhibited by astodrimer sodium. Astodrimer sodium did not prevent attachment of the SARS-CoV-2 VOC α and β spike S1, or γ RBD spike protein, to the ACE2 receptor in vitro.

**Conclusion:** Astodrimer sodium mimics negatively charged glycosaminoglycans and provides a potent antiviral and virucidal barrier to viral attachment and entry. The potent broad-spectrum anti-pandemic coronavirus

and virucidal efficacy of astodrimer sodium against whole virus is likely due to blocking multiple electrostatic interactions of the spike protein that are not negated by minor or major changes to the isolated RBD of SARS-CoV-2 VOC α, β and γ alone. Astodrimer sodium has the potential to block the binding of pan-SARS-CoV-2, thus reducing the potential for the development of COVID-19.

| SARS-CoV-2 : Astodrimer Sodium (10 mg/mL) Incubation Time | Percent Reduction of Infectious Progeny SARS-CoV-2 vs Untreated Virus Control* | | | | | |
|---|---|---|---|---|---|---|
| | USA-WA-1/2020 | Alpha | Beta | Gamma | Delta | Kappa |
| 30 seconds | >99.9% | >99.9% | >99% | >99% | >99.99% | >99.9% |
| 1 minute | >99.9% | >99.9% | >99% | >99% | >99.99% | >99.9% |
| 5 minutes | >99.9% | >99.99% | >99.9% | >99.9% | >99.99% | >99.9% |
| 15 minutes | >99.99% | >99.99% | >99.99% | >99.99% | >99.999% | >99.99% |
| 30 minutes | >99.99% | >99.99% | >99.99% | >99.99% | >99.999% | >99.99% |

## 479 LONG-ACTING CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS: ATLAS-2M WEEK 152 RESULTS

**Edgar T. Overton**[1], Gary Richmond[2], Giuliano Rizzardini[3], Anders Thalme[4], Pierre-Marie Girard[5], Alexander Wong[6], Norma Porteiro[7], Carlos Español[8], Carolina Acuipil[9], Asma Aksar[10], Yuanyuan Wang[11], Ronald D'Amico[12], Christine Talarico1[2], Kati Vandermeulen[13], William R. Spreen1[2]

*[1]University of Alabama at Birmingham, Birmingham, AL, USA, [2]Nova Southeastern University, Fort Lauderdale, FL, USA, [3]Fatebenefratelli Sacco Hospital, Milan, Italy, [4]Karolinska University Hospital, Stockholm, Sweden, [5]University of Paris, Paris, France, [6]University of Saskatchewan, Regina, Canada, [7]Fundacion IDEAA, Buenos Aires, Argentina, [8]GlaxoSmithKline, Brentford, UK, [9]GlaxoSmithKline, Buenos Aires, Argentina, [10]GlaxoSmithKline, Manchester, UK, [11]GlaxoSmithKline, Collegeville, PA, USA, [12]ViiV Healthcare, Research Triangle Park, NC, USA, [13]Janssen, Beerse, Belgium*

**Background:** Cabotegravir (CAB) + rilpivirine (RPV) dosed intramuscularly monthly or every 2 months is a complete long-acting (LA) regimen for the maintenance of HIV-1 virologic suppression. The ATLAS-2M (NCT03299049) Week (W) 48 primary and W96 secondary analyses demonstrated noninferiority of CAB+RPV LA administered every 8 weeks (Q8W) vs. every 4 weeks (Q4W). Here, we report the W152 results.

**Methods:** ATLAS-2M is a Phase IIIb, randomized, multicenter study assessing the efficacy and safety of CAB+RPV LA Q8W vs. Q4W. Virologically suppressed (HIV-1 RNA <50 copies/mL) individuals receiving CAB+RPV LA Q4W (ATLAS [NCT02951052] study rollover) or oral therapy were randomized 1:1 to receive CAB+RPV LA Q8W or Q4W. The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 copies/mL (FDA Snapshot; 4% noninferiority margin). Other endpoints included proportion of participants with plasma HIV-1 RNA <50 copies/mL, incidence of confirmed virologic failure (CVF; two consecutive plasma HIV-1 RNA ≥200 copies/mL), tolerability, and safety.

**Results:** 1045 participants received CAB+RPV LA (Q8W, n=522; Q4W, n=523). Median (range) age was 42 years (19–83); 27% were female (sex at birth) and 73% were White. At W152, CAB+RPV LA Q8W demonstrated noninferior efficacy vs. Q4W dosing, with 2.7% (n=14) and 1.0% (n=5) of participants having HIV-1 RNA ≥50 copies/mL in each arm, and the confidence interval excluded the noninferiority margin (Table). High levels of virologic suppression were observed; 86–87% of participants maintained HIV-1 RNA <50 copies/mL. Further, 11 (2.1%) and 2 (0.4%) participants in the Q8W and Q4W arms had CVF, representing an additional 2 since the W96 analysis. Both were in the Q8W arm and had treatment-emergent resistance-associated mutations to RPV (E138A+Y181Y/C; E138A+M230M/L) and CAB (Q148R). Safety profiles were comparable, with no new significant safety information observed. Injection site reactions were the most common adverse event; most were mild or moderate in severity (98.9%), with a median duration of 3 days, and few participants discontinued due to injection-related reasons.

**Conclusion:** Efficacy of CAB+RPV LA Q8W continued to be noninferior to Q4W at W152, with both regimens maintaining high levels of virologic suppression. The overall incidence of CVF was low, with two additional cases reported in the Q8W arm after W96. These data further support CAB+RPV LA as a complete regimen for the maintenance of HIV-1 virologic suppression.

**Table. ATLAS-2M Key Results at Week 96 and Week 152 Analysis Timepoints**

| ITT-E population n (%) | Week 96 | | Week 152 | |
|---|---|---|---|---|
| | Q8W (n=522) | Q4W (n=523) | Q8W (n=522) | Q4W (n=523) |
| **Primary endpoint** HIV-1 RNA ≥50 c/mL (FDA Snapshot) | 11 (2.1) | 6 (1.1) | 14 (2.7) | 5 (1.0) |
| Adjusted difference* (95% CI) | 1.0 (–0.6, 2.5) | | 1.7 (0.1, 3.3)† | |
| Data in window not <50 c/mL | 2 (0.4) | 2 (0.4) | 1 (0.2) | 0 (0) |
| Discontinued for lack of efficacy | 8 (1.5) | 3 (0.6) | 12 (2.3) | 4 (0.8) |
| Discontinued for other reason while not <50 c/mL | 1 (0.2) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| No virologic data | 36 (6.9) | 45 (8.6) | 52 (10.0) | 69 (13.2) |
| Discontinued due to AE or death | 17 (3.3) | 17 (3.3) | 23 (4.4) | 24 (4.6) |
| Discontinued for other reason | 16 (3.1) | 27 (5.2) | 28 (5.4) | 44 (8.4) |
| On study but missing data in window | 3 (0.6) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| **Key secondary efficacy endpoint** HIV-1 RNA <50 c/mL (FDA Snapshot) | 475 (91.0) | 472 (90.2) | 456 (87.4) | 449 (85.9) |
| Adjusted difference* (95% CI) | 0.8 (–2.8, 4.3) | | 1.5 (–2.6, 5.6) | |
| **Safety summary‡** | | | | |
| All AEs | 488 (93.5) | 499 (95.4) | 503 (96.4) | 508 (97.1) |
| Grade 2–5 drug-related AEs | 178 (34.1) | 187 (35.8) | 195 (37.4) | 210 (40.2) |
| Serious AEs | 33 (6.3) | 28 (5.4) | 49 (9.4) | 44 (8.4) |
| AEs leading to discontinuation | 18 (3.4) | 19 (3.6) | 23 (4.4) | 25 (4.8) |
| Discontinued for ISR-related reason | 7 (1.3) | 11 (2.1) | 8 (1.5) | 13 (2.5) |
| Number of injections | 12,832 | 23,855 | 20,563 | 39,478 |
| Number of ISR events | 3400 | 4157 | 4168 | 5494 |
| Median ISR duration, days | 3 | 3 | 3 | 3 |

*Adjusted for prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).
†The Week 152 per protocol analysis adjusted treatment difference between treatment arms is 1.4% [–0.2, 2.9].
‡Day 1 until the end of the Maintenance Phase for the Week 96 columns; Day 1 to Week 152 analysis for the Week 152 columns.
AE, adverse event; CAB, cabotegravir; CI, confidence interval; ISR, injection site reaction; ITT-E, intention-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

## 480 SWITCHING TO A NRTI-FREE 2 DRUG REGIMEN (2DR) – A SUB-ANALYSIS OF THE DUALIS STUDY

**Malte B. Monin**[1], Christiane Cordes[2], Schneider Jochen[3], Hans-Jürgen Stellbrink[4], Stefan H. Scholten[5], Björn Jensen[6], Heiko Jessen[7], Wilfried Obst[8], Petra Spornraft-Ragaller[9], Pavel Khaykin[10], Annamaria Balogh[11], Eva Wolf[11], Helen Binder[3], Christoph Spinner[3], Christoph Boesecke[1]

*[1]Bonn University Hospital, Bonn, Germany, [2]Private Practice, Berlin, Germany, [3]Technical University of Munich, School of Medicine, Munich, Germany, [4]ICH Study Center, Hamburg, Germany, [5]Private Practice, Cologne, Germany, [6]University Hospital Düsseldorf, Bonn, Germany, [7]Praxis Jessen2+Kollegen, Berlin, Germany, [8]University of Magdeburg, Magdeburg, Germany, [9]University of Dresden, Dresden, Germany, [10]Private Practice, Frankfurt, Germany, [11]MUC Research, Munich, Germany*

**Background:** Switching from a three-drug regimen (3DR: boosted darunavir [bDRV] and two nucleoside reverse transcriptase inhibitors [NRTIs]) to a two-drug regimen (2DR: bDRV and dolutegravir) demonstrated non-inferiority with regard to viral suppression in people living with HIV (PLWH) in the DUALIS study. This sub-analysis focuses on changes in metabolic and renal parameters when sparing the NRTI backbone.

**Methods:** DUALIS was a randomized, open-label, multicenter (27) Phase III-trial. Participants were virologically suppressed (HIV-RNA < 50 copies/mL) on 3DR for at least 24 weeks. Data of metabolic and renal parameters at baseline and week 48 were compared.

**Results:** PLWH on 2DRs gained +2.0 kg in body weight (-0.2 to +0.4) versus +0.2 kg (-1.9 to +2.1) on 3DRs (p= 0.0006). The BMI increased by +0.6 kg/ $m_2$ (-0.1 to +1.2 kg/ $m_2$) and +0.1 kg/ $m_2$ (-0.5 to +0.7 kg/ m2), respectively (p= 0.0006). Total cholesterol increased by + 20.0 mg/ dL (+3.0 to +35.5 mg/ dL) on 2DRs versus no increase (-18.0 to +15.5 mg/ dL) on 3DRs (p< 0.001). The LDL-fraction increased by + 13.3 mg/ dL (-3.0 to +31.3 mg/ dL) and the HDL-fraction by +4.9 mg/ dL (-1.0 to +10.4 mg/ dL) on 2DRs, whereas the LDL-fraction was stable (-14.0 to +18.0 mg/ dL) and the HDL-fraction decreased by -1.0 mg/ dL (-5.0 to +4.0 mg/ dl) on 3DRs (p< 0.001). The MDRD-eGFR decreased by – 7,8 mL/min/1.73 $m_2$ (-17.4 to -0.3 mL/min/1.73 $m_2$) on 2DRs versus -0.4 mL/min/1.73 $m_2$ (-8.8 to +5.7 mL/min/1.73 $m_2$) on 3DRs (p=0.0002). Potential creatinine-based eGFR alterations under dolutegravir were considered regarding serum levels of cystatin C. There was no increase at 0.0 mg/L in both arms (2DR -0.1 to +0.1 mg/L and 3DR 0.0 to +0.1 mg/L). In the 3DR arm, a switch to the tenofovir alafenamid-backbone during the study period resulted in an increase in body weight by +0.5 (-0.8 to +4.0) kg and in BMI by +0.2 (-0.3 to +1.2) kg/ $m_2$. When remaining on tenofovir disoproxil, the body weight as well as the BMI were stable (body weight: -2.1 to +2.0 kg; BMI: -0.7 to +0.6). The LDL-fraction changed by + 8.0 (-3.0 to +27.0) mg/dL on TAF versus -1.0 (-14.0 to +16.0) mg/dL on TDF (p=0.1043).

**Conclusion:** While being non-inferior in terms of viral suppression, sparing the NRTI backbone showed no advantages in metabolic or renal parameters over 48 weeks.

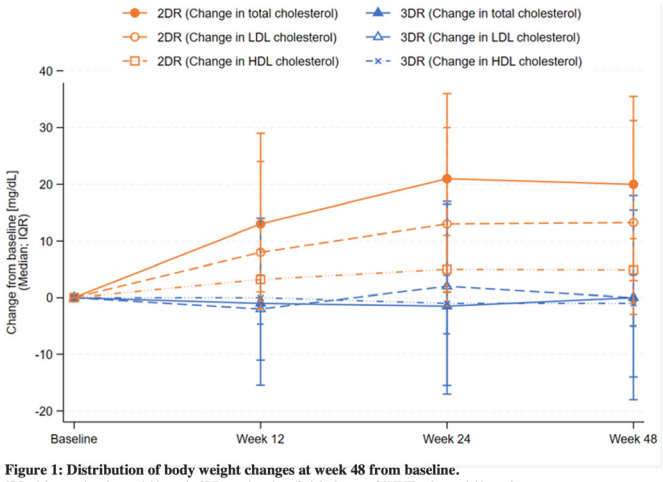



**Figure 1: Distribution of body weight changes at week 48 from baseline.**
2DR, dolutegravir + darunavir/ritonavir; 3DR, continuation of triple therapy of 2NRTI + darunavir/ritonavir.

## 481 ARCHIVED RESISTANCE AND RESPONSE TO <40 C/ML & TND – DTG/3TC FDC AT WEEK 48 IN SALSA

**Mark Underwood**[1], Olayemi Osiyemi[2], Rafael Rubio[3], Laurent Hocqueloux[4], Norma Porteiro[5], Olaf Degen[6], James Oyee[7], Joe Horton[8], Chris Parry[9], Ruolan Wang[1], Myooran Sithamparanathan[9], Jean A. Van Wyk[9], Brian Wynne[1], Choy Man[1], Elizabeth Blair[1]

*[1]ViiV Healthcare, Research Triangle Park, NC, USA, [2]Triple O Research Institute, West Palm Beach, FL, USA, [3]Hospital Universitario 12 de Octubre, Madrid, Spain, [4]Centre Hospitalier Régional d'Orléans, Orléans, France, [5]Fundacion IDEAA, Buenos Aires, Argentina, [6]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, [7]GlaxoSmithKline, Brentford, UK, [8]Parexel International, Durham, NC, USA, [9]ViiV Healthcare, Brentford, UK*

**Background:** The SALSA study showed switching to DTG/3TC FDC was non-inferior to continuing current antiretroviral regimen (CAR) at Week 48, with 94% (232/246) vs 93% (229/247) having HIV-1 RNA viral load (VL) <50 c/mL by FDA Snapshot algorithm. This post-hoc analysis assesses proportion of baseline (BL) participant samples with archived resistance, and virologic response through 48 weeks using the stringent VL measure <40 c/mL and target not detected (TND).

**Methods:** Adults with VL <50 c/mL for ≥6 months without evidence of virologic failure were randomized to DTG/3TC FDC or continued CAR. Historic genotypic resistance results were submitted if available, and participants were excluded if IAS 2019 DTG-associated or major NRTI resistance was present. RealTime HIV-1 assay provided quantitative VL from 40 to 10,000,000 c/mL, and qualitative target detected (TD) or TND data for VL <40 c/mL. TND at last available on-treatment VL was assessed for participants with BL proviral genotype data from Monogram Biosciences Genosure Archive assay, at least 1 post-BL on-treatment VL result, and not meeting protocol deviation.

**Results:** Of 246 and 247 participants randomized to the DTG/3TC and CAR groups, respectively, BL proviral DNA genotypes were generated for 196/224 and 189/216 available samples. Time from first ART to study start for those with BL genotypes available (excluding 4 protocol deviators per arm) was [median (range)] 66.1 (4,240) and 74.4 (12,253) months. Overall proportions with TND at last available on-treatment VL in DTG/3TC and CAR groups were 155/192 (81%) and 153/185 (83%), respectively. Participants in the DTG/3TC and CAR groups, respectively, had 15 (8%) vs 16 (9%) major NRTI mutations, 28 (15%) vs 17 (9%) major NNRTI, 14 (7%) vs 12 (6%) major PI, 1 (<1%) vs 4 (2%) major InSTI, and 8 (4%) vs 5 (3%) minor InSTI mutations. Frequencies for TND through 48 weeks by BL mutation were broadly similar across groups (Table). M184V/I was present in 5 (3%) participants in both the DTG/3TC and CAR groups, all with VL <40 c/mL and, respectively, 4/5 vs 3/5 having VL <40 c/mL and TND at Week 48.

**Conclusion:** Using a more stringent measure of VL <40 c/mL and TND, responses for DTG/3TC vs CAR were similar despite BL archived proviral resistance, including M184V/I present in BL testing at 3%. These data, as well as prior reported responses using <50 c/mL for DTG/3TC vs CAR (SALSA) or TAF-based regimen (TANGO study), are supportive of the efficacy and potency of DTG/3TC in suppressed switch participants.

**Table.** Most Frequent BL IAS Resistance by Class and TND Frequencies for Last On-Treatment VL

| | DTG/3TC (N=192) | | CAR (N=185) | | | DTG/3TC (N=192) | | CAR (N=185) | |
|---|---|---|---|---|---|---|---|---|---|
| Category | n (%)[a] | TND (%) | n (%) | TND (%) | Category | n (%) | TND (%) | n (%) | TND (%) |
| NRTI total[b] | 15 (8%) | 13 (87%) | 16 (9%) | 11 (69%) | INSTI major total[d] | 1 (<1%) | 1 (100%) | 4 (2%) | 4 (100%) |
| Any TAM | 7 (4%) | 6 (86%) | 5 (3%) | 4 (80%) | Y143H | 1 (<1%) | 1 (100%) | 2 (1%) | 2 (100%) |
| A62V | 5 (3%) | 4 (80%) | 4 (2%) | 3 (75%) | Q148R | 0 | NA | 1 (<1%) | 1 (100%) |
| M184V | 5 (3%) | 4 (80%) | 4 (2%) | 2 (50%) | Y143C | 0 | NA | 1 (<1%) | 1 (100%) |
| M184I | 0 | NA | 1 (<1%) | 1 (100%) | INSTI minor total[d] | 8 (4%) | 8 (100%) | 5 (3%) | 4 (80%) |
| NNRTI total[c] | 28 (15%) | 21 (75%) | 17 (9%) | 13 (76%) | T97A | 3 (2%) | 3 (100%) | 5 (3%) | 4 (80%) |
| PI total[c] | 14 (7%) | 13 (93%) | 12 (6%) | 9 (75%) | E138K | 2 (1%) | 2 (100%) | 0 | NA |

Mutations are from Sep/Oct IAS 2019. NA is not applicable.
[a]Denominators are those with BL proviral genotype generated. [b]NRTI totals count participants with at least one major NRTI mutation, including in the TAMs subgroup. TAM totals contain at least one TAM mutation. NRTI mutations with overall across arm frequency <1% are not included, except for key M184I. [c]Only totals are shown for NNRTI and PI IAS major resistance. [d]All INSTI major and minor mutations >1% are included.

## 482 2DR VS 3DR INTEGRASE INHIBITOR-BASED REGIMENS INITIATION AND CD4+/CD8+ RATIO RECOVERY

**Javier Martínez-Sanz**[1], Raquel Ron[1], Elena Moreno[1], Matilde Sánchez-Conde[1], Alfonso Muriel[1], María Rivero[2], José-Ramón Blanco[3], Enrique Bernal[4], Miguel de Zárraga[5], Maria José Galindo[6], Eva Poveda[7], Gloria Samperiz[8], Santiago Moreno[1], Sergio Serrano-Villar[1]

*[1]Hospital Ramón y Cajal, Madrid, Spain, [2]Complejo Hospitalario de Navarra, Pamplona, Spain, [3]Hospital San Pedro, La Rioja, Spain, [4]Hospital Universitario Reina Sofia, Murcia, Spain, [5]Hospital San Agustín, Avilés, Spain, [6]Hospital Clinic of Valencia, Valencia, Spain, [7]Hospital Universitario Alvaro Cunqueiro, Vigo, Spain, [8]Hospital Universitario Miguel Servet, Zaragoza, Spain*

**Background:** Accumulating evidence suggests that integrase strand-transfer inhibitors (InSTI)-based initial antiretroviral therapy (ART) results in greater CD4/CD8 ratio recovery compared to other regimens. However, it is unknown whether the treatment initiation with InSTI-based two-drug regimens (2DR) has a different impact on the CD4/CD8 ratio recovery compared to InSTI-based 3DR.

**Methods:** We emulated a target trial to assess the effect of two different ART strategies on CD4/CD8 ratio normalization. We included all subjects included in the Cohort of the Spanish HIV Research Network (CoRIS) who started 2DR with dolutegravir (DTG) plus 3TC or 3DR based on bictegravir or DTG. We matched each participant who started 2DR with up to four participants who received 3DR based on age, sex, transmission category, educational level, country of origin, baseline HIV RNA, AIDS diagnosis, and pre-ART nadir CD4/CD8 ratio. Subsequently, we fitted generalized estimating equation (GEE) models to allow for clustered data analysis, to assess the risk of CD4/CD8 ratio normalization at 48 weeks for three different cutoffs (0.5, 1.0 and 1.5).

**Results:** A total of 485, 805, and 924 participants were matched for each of the three analyses (cutoffs of 0.5, 1.0, and 1.5, respectively). The distribution of covariates was similar in the three models. Overall, the study sample was representative of a medium-aged population (median age 37 years) with a higher representation of men (88%) and a median CD4/CD8 ratio around 0.30. No participant presented virological failure during follow-up. At 48 weeks, 45% of participants achieved a CD4/CD8 ratio >0.5, 15% achieved a ratio >1.0, and 6% achieved a ratio >1.5 (Figure 1). After matching according to the covariates of interest, GEE models yielded a similar risk of reaching a CD4/CD8 ratio >0.5 (OR 1.00, 95% CI 0.67 - 1.50), CD4/CD8 >1.0 (OR 1.03, 95% CI 0.68 - 1.58), and CD4/CD8 >1.5 (OR 0.86, 95% CI 0.48 - 1.54) between both treatment strategies. Figure 1 shows Kaplan-Meier survival plots of estimated overall CD4/CD8 normalization. There were no differences between 2DR and 3DR in the incidence ratio of CD4/CD8 ratio normalization at any of the cutoffs.

**Conclusion:** This study provides new evidence that CD4/CD8 ratio recovery rates are similar during the first 48 weeks after ART initiation with 2DR or 3DR InSTI-based therapies. Next studies should address the potential long-term differences between these strategies.

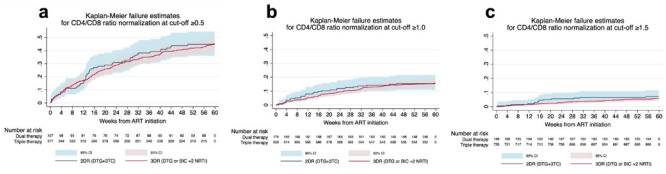



**Figure 1. Kaplan-Meier survival estimates for CD4/CD8 ratio normalization at 0.5, 1, and 1.5 cutoffs in participants with 2DR and 3DR.**
The graph shows survival estimates for CD4/CD8 normalization for the 0.5 (a), 1.0 (b) and 1.5 (c) cutoff points, during the 48 + 12 weeks of follow-up. The p-values were obtained using the log-rank test.
*Abbreviations: 2DR, two-drug regimens; 3DR, three-drug regimens; BIC, bictegravir; DTG, dolutegravir; NRTI, nucleoside reverse transcriptase inhibitor.*

## 483 MULTIOMICS PLASMA PROFILE OF SWITCHING FROM 3DR TO DOLUTEGRAVIR PLUS LAMIVUDINE

**Anna Rull**[1], Elisa de Lazzari[2], Eugenia B. Negredo[3], Pere Domingo[4], Juan M. Tiraboschi[5], Esteve Ribera[6], Nadia Abdulghani[7], Verònica Alba[1], Consuelo Viladés[1], Joaquin Peraire[1], Jose M. Gatell[8], Jose L. Blanco[2], Francesc Vidal[1], Esteban Martinez[2]

*[1]Hospital Universitario de Tarragona Joan XXIII, Tarragona, Spain, [2]Hospital Clinic of Barcelona, Barcelona, Spain, [3]Hospital Germans Trias i Pujol, Barcelona, Spain, [4]Hospital de Sant Pau, Barcelona, Spain, [5]Hospital Universitario de Bellvitge, Barcelona, Spain, [6]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [7]Hospital Arnau de Vilanova, Lleida, Spain, [8]Universitat de Barcelona, Barcelona, Spain*

**Background:** The DOLAM trial revealed that switching from triple ART (3DR) to dolutegravir plus lamivudine resulted virologically non-inferior and as safe as continuing triple ART (Lancet HIV2021; 8:e463-73). At 48 weeks, people living with HIV (PLWH) switching from 3DR to dolutegravir plus lamivudine had a higher weight gain compared to those continuing 3DR (1.5Kg [0.5-2.5], p=0.05) but no significant changes in fasting glucose and lipids. Multiomics plasma profile was performed to gain insight on whether some pathways might be affected by this therapy switch.

**Methods:** DOLAM (EudraCT 201500027435) is a Phase IV, randomised, open-label, non-inferiority trial, done at six HIV clinics in Catalonia, Spain. PLWH receiving a 3DR regimen were assigned (1:1) to switch to oral dolutegravir 50 mg and lamivudine 300 mg once daily or to continue 3DR for 48 weeks. Untargeted proteomics, metabolomics and lipidomics analyses were performed at baseline and at 48 weeks. Univariate and multivariate analyses were performed to identify 48-week changes in key molecules between both study arms. Differentially expressed proteins were selected as input in the STRING database to predict protein-protein interactions and to establish which biological processes could be affected.

**Results:** Untargeted proteomic, metabolomic and lipidomic analyses identified 136 proteins, 97 metabolites and 117 lipid species. In an exploratory analysis, PLWH who switched to dolutegravir plus lamivudine showed higher plasma ornithine levels (P=0.033). Also, patients who switched had higher plasma hemoglobin subunit alpha (p=0.044), insulin-like growth factor-binding protein 3 (p=0.026) and lipopolysaccharide-binding protein (p=0.03) concentrations. Of interest, the later three proteins revealed a network of predicted functional associations related to the regulation of cell death (RCD, false discovery rate = 0.03, Figure 1).

**Conclusion:** Multiomic approach identified some soluble parameters involved on metabolic pathways in PLWH switching from 3DR to dolutegravir plus lamivudine. Preliminary data suggests that switching may activate metabolomics pathways of energy consumption giving an antifatigue effect (Ornithine). Signaling cascades and molecular effectors for the preservation of a biological equilibrium (RCD) may play an essential role for tissue homeostasis when switching from 3DR to dolutegravir plus lamivudine.

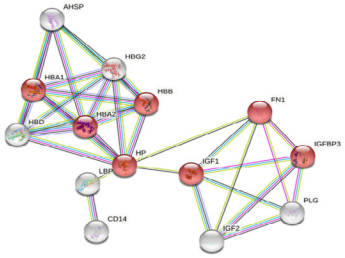



**Figure 1.** Network of protein interaction generated with the set of three proteins that resulted significantly higher in the study regimen at 48 weeks. The names of soluble protein markers were used as input in the STRING database. Colored proteins were identified in the regulation of cell death biological pathway.

## 484 LOW-LEVEL HIV REPLICATION FOR DTG/3TC VS TAF-BASED REGIMEN IN TANGO THROUGH WEEK 144

**Ruolan Wang**[1], Nisha George[2], Mounir Ait-Khaled[3], Andrew Tomlinson[4], James Oyee[4], Thomas Lutz[5], Olayemi Osiyemi[6], Miguel Górgolas[7], Riya Moodley[3], Brian Wynne[1], Myooran Sithamparanathan[3], Mark Underwood[1]

*[1]ViiV Healthcare, Research Triangle Park, NC, USA, [2]GlaxoSmithKline, Bangalore, India, [3]ViiV Healthcare, Brentford, UK, [4]GlaxoSmithKline, Brentford, UK, [5]Infektio Research, Frankfurt, Germany, [6]Triple O Research Institute, West Palm Beach, FL, USA, [7]Jiménez Díaz Foundation University Hospital, Madrid, Spain*

**Background:** The TANGO study demonstrated non-inferior virologic efficacy (HIV-1 RNA ≥50 c/mL by Snapshot algorithm) of switching to a 2DR of DTG/3TC vs continuing 3-or 4-drug TAF-based regimens (TBR) in virologically suppressed adults with HIV-1 at 144 weeks. Abbott RealTime HIV-1 assay measures viral load (VL) from 40 to 10,000,000 c/mL and provides qualitative target detected (TD) or target not detected (TND) outcomes for VL <40 c/mL. VL <50 c/mL has unknown clinical influence, and low-level viremia may depend on pre-treatment VL and proviral DNA load set-points. Previous assessment of low-level viremia using TND/TD measures showed that more participants on DTG/3TC than those continuing TBR had TND at all visits through Week 96. We present here longer-term HIV-1 RNA data with TD/TND and elevated VL through Week 144 (WK144).

**Methods:** Proportions of participants with VL <40 c/mL and TND status were analyzed by visit (Snapshot) through WK144. Participants' TD/TND status over time, overall and by baseline VL classifications, was assessed. The frequency of elevated VL (VL ≥50 c/mL) categories including "blips" was also determined.

**Results:** At WK144, similar proportions of participants had TND in the DTG/3TC and TBR arms (76% [279/369] vs 72% [267/372], respectively; adjusted difference using Cochran-Mantel-Haenszel method, 3.9%; 95% CI: −2.5, 10.2 by Snapshot) and proportions were also similar at each visit. Across baseline VL categories, proportions with TND at all visits through WK144 were 33% (123/369) in DTG/3TC arm vs 27% (101/372) in TBR arm (Table). More participants with TND at baseline had post-baseline TND at all visits compared with participants with higher baseline VL categories. The occurrence of elevated VL events remained low and similar across arms through WK144: 8% (28/369) in DTG/3TC arm vs 11% (42/372) in TBR arm. The most frequently observed VL rebounds were "blips" with 5% in DTG/3TC arm and 7% in TBR arm. None of the 7 participants (4 on DTG/3TC vs 3 on TBR) with archived M184V/I experienced an elevated VL event through WK144.

**Conclusion:** The proportions of participants with VL <40 c/mL and TND by visit were high and comparable between treatment arms. Similar proportions of participants across both arms maintained post-baseline TND at all available visits through WK144 and >90% of participants with TND at baseline never had a VL ≥40 c/mL. These long-term virology data continue to demonstrate the potency and durability of DTG/3TC compared to 3DR in maintaining viral suppression.

**Table.** Changes in Quantifiable and Non-quantifiable VL Levels by Baseline VL Category Through Week 144

| | | DTG/3TC (N=369) | | | TBR (N=372) | | |
|---|---|---|---|---|---|---|---|
| | | TND | TD | ≥40 c/mL | TND | TD | ≥40 c/mL |
| | Baseline | n[a]=302 (82%) | n[a]=51 (14%) | n[a]=11 (3%) | n[a]=303 (81%) | n[a]=59 (16%) | n[a]=9 (2%) |
| Post-baseline | At least one VL ≥50 c/mL[b,c] | 19 (6%) | 7 (14%) | 2 (18%) | 32 (11%) | 9 (15%) | 1 (11%) |
| | At least one 40≤ VL <50 c/mL[b] | 5 (2%) | 5 (10%) | 2 (18%) | 11 (4%) | 5 (8%) | 1 (11%) |
| | At least one VL<40 c/mL and TD[b] | 161 (53%) | 33 (65%) | 7 (64%) | 166 (55%) | 39 (66%) | 6 (67%) |
| | All VLs <40 c/mL and TND[b] | 117 (39%) | 6 (12%) | 0 (0%) | 94 (31%) | 6 (10%) | 1 (11%) |

Post-baseline categories are mutually exclusive and determined by highest VL observed. Five participants with baseline VL <40 c/mL in DTG/3TC arm and 1 participant with baseline VL ≥50 c/mL in TBR arm not presented due to no post-baseline VL data.
[a]n: Participants with post-baseline VL data (percentages based on N). [b]Percentages based on n. [c]"Blips," defined as VLs between 50 ~ <200 c/mL with adjacent VL value of <50 c/mL, are included in this category.

## 485 SWITCHED VERSUS RECYCLED nRTIs IN PI-BASED SECOND-LINE REGIMENS IN EAST AFRICA

**Suzanne McCluskey**[1], Beverly Musick[2], Arvind Kaimal[3], Francesca Odhiambo[4], Lameck Diero[5], Winnie R. Muyindike[6], Rita Lyamuya[7], Samson Okumu[8], Mark Siedner[1], Kara Wools-Kaloustian[2], Constantin Yiannoutsos[2]

*[1]Massachusetts General Hospital, Boston, MA, USA, [2]Indiana University, Indianapolis, IN, USA, [3]Infectious Diseases Institute, Kampala, Uganda, [4]Kenya Medical Research Institute-UCSF Infectious Disease Research Training Program, Kisumu, Kenya, [5]Moi University, Eldoret, Kenya, [6]Mbarara University of Science and Technology, Mbarara, Uganda, [7]Morogoro Regional Hospital, Morogoro, Tanzania, [8]Masaka HIV Care Clinic, Masaka, Uganda*

**Background:** World Health Organization guidelines recommend switching nucleoside reverse transcriptase inhibitors (NRTIs) in second-line antiretroviral therapy (ART) after first-line failure. Recent clinical trial data suggest that recycling NRTIs in protease inhibitor (PI)-based second-line ART may have similar efficacy to switched NRTIs. We evaluate this question using programmatic data from East Africa.

**Methods:** We analyzed data from the East Africa International Epidemiology Databases to Evaluate AIDS, which includes programmatic data from public sector clinics in Kenya, Tanzania, and Uganda. We included adults (age ≥18 years) with HIV who were switched to atazanavir or lopinavir-based second-line

ART after virologic failure on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line ART containing zidovudine (AZT) or tenofovir (TDF). Individuals were included if a switch to second-line ART occurred after introduction of routine viral load testing at the relevant clinic and if ≥1 year of post-switch observation time was available. Our outcome of interest was 1-year crude cumulative incidence of viral suppression (HIV-1 RNA <1,000 copies/mL) after switch. We compared individuals with switched versus recycled NRTIs in their second-line regimen, accounting for competing risks of death, lost to follow-up, or transfer. Among those with recycled NRTIs, we compared cumulative incidence of viral suppression for those with recycled TDF versus AZT via Gray's test.

**Results:** Of 3,240 participants analyzed, median age was 40 (IQR 33 – 47) at the time of switch, and 66% were female. Only 7% (n = 212/3,240) had recycled NRTIs in their second-line regimen, of which 79% (n = 167/212) used recycled TDF. Crude cumulative incidence of viral suppression one year after switch to second-line was 60% (95% CI 53-67%) among those with recycled NRTIs and 69% (95% CI 67-70%) in those with switched NRTIs (p-value = 0.019). Among those with recycled NRTIs, there was no difference in viral suppression rates for those with recycled TDF versus AZT (p-value = 0.901). Limitations include possible confounding by indication since clinical reasons for use of recycled NRTI regimens for participants in this analysis are not known.

**Conclusion:** In programmatic care in East Africa, we found improved rates of virologic suppression among individuals switching NRTIs in PI-based second-line ART. Recommendations for second-line PI-based regimens with recycled NRTIs should be made with close observation of clinical outcomes.

## 486 RESUPPRESSION AFTER VIROLOGICAL FAILURE IN DOLUTEGRAVIR AND EFAVIRENZ-BASED REGIMENS

**Kaitlyn Mccan**[1], Francois Venter[2], Eric Delaporte[3], Simiso M. Sokhela[2], Charles Kouanfack[4], Godspower Akpomiemie[5], M. Mpoudi-Etame[6], Angela Tembo[5], Tamara Tovar Sanchez[7], P. Omgba Bassega[8], Ambar Qavi[1], Andrew Hill[9]
*[1]Imperial College London, London, UK, [2]Ezintsha, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa, [3]TransVIHMI, University of Montpellier, IRD, INSERM, Montpellier, France, [4]University of Dschang, Cameroon, Cameroon, [5]University of Witwatersrand, Johannesburg, South Africa, [6]Military Hospital Region N°1, Yaoundé, Cameroon, [7]University of Montpellier, Montpellier, France, [8]Cité Verte District Hospital, Yaoundé, Cameroon, [9]University of Liverpool, Liverpool, UK*

**Background:** Dolutegravir (DTG) and other integrase inhibitor (InSTI) based treatments are highly effective, tolerable, and have high barriers to genetic resistance. Participants who display virological rebound on DTG-based regimens may be able to re-suppress with adherence counselling, without the risk of developing resistance and preventing switches to less tolerable or more expensive alternatives. The following analysis aims to assess the re-suppression rate following virological rebound of participants on DTG and efavirenz (EFV) based regimens in ADVANCE and NAMSAL.

**Methods:** In ADVANCE, 1,053 treatment-naïve participants in South Africa were randomized to TAF/FTC+DTG, TDF/FTC+DTG, or TDF/FTC/EFV600. In NAMSAL, 616 treatment-naïve participants in Cameroon were randomized to TDF/FTC+DTG or TDF/FTC/EFV400. A virological rebound (VR) event was defined as HIV-RNA >1,000 copies/mL occurring after a participant's first undetectable reading. Following each VR event, three subsequent HIV-RNA readings were assessed to determine the proportion of events which lead to re-suppression (HIV-RNA <50 copies/mL). Participants were classified as either suppressed, unsuppressed or no follow up data. In each trial, differences between the DTG and EFV arms were tested using two sample tests of proportions. Development of drug resistance was assessed in participants with a VR event.

**Results:** There was a similar number of VR-events >1,000 copies/mL in ADVANCE and NAMSAL (Table 1). In ADVANCE, the percentage of participants who re-suppressed <50 copies/mL within 3 subsequent readings was 62%, 66%, and 37% for TAF/FTC+DTG, TDF/FTC+DTG, and TDF/FTC/EFV respectively, with significant differences between the DTG and EFV groups (p<0.01). In NAMSAL, the percentage of re-suppression was 53% and 30% for participants on TDF/FTC+DTG and TDF/FTC/EFV treatments respectively (p<0.01). In ADVANCE and NAMSAL, participants on DTG-based regimens showed little development of resistance following VR events compared to participants on EFV based treatment.

**Conclusion:** In ADVANCE and NAMSAL, participants taking DTG regimens with HIV RNA >1,000 copies/mL after being suppressed were more likely to resuppress without a change in treatment with low rates of resistance. EFV based regimens were more likely to show sustained viremia and higher resistance compared to DTG based regimens.

***Summary of results in ADVANCE and NAMSAL***

| | ADVANCE | | | NAMSAL | |
|---|---|---|---|---|---|
| | TAF/FTC+DTG | TDF/FTC+DTG | TDF/FTC/EFV600 | TDF/FTC+DTG | TDF/FTC/EFV |
| **Baseline Characteristics** | | | | | |
| HIV-1 viral load | | | | | |
| Median (IQR) – log10 copies/ml | 4.4(3.8-4.9) | 4.4(3.8-4.9) | 4.4(3.7-4.9) | 5.3 (4.8-5.8) | 5.3 (4.7-5.8) |
| ≥ 100,000 copies/ml - n (%) | 66 (19) | 62 (18) | 72 (8) | 207 (67) | 200 (66) |
| ≥ 500,000 copies/ml - n (%) | 11 (3) | 9 (3) | 8 (3) | 93 (30) | 95 (31) |
| Median CD4+ T-cell count (IQR) - per mm$^3$ | 323 (174-493) | 276 (164-428) | 298 (177-445) | 289 (157-452) | 271 (147-427) |
| CD4+ T-cell count | | | | | |
| < 200 per mm$^3$ - n (%) | 101 (29) | 114 (32) | 104 (30) | 97 (31) | 107 (35) |
| 200-349 per mm$^3$ - n (%) | 90 (26) | 113 (32) | 107 (30) | 89 (29) | 88 (29) |
| 350-499 per mm$^3$ - n (%) | 76 (22) | 59 (17) | 76 (22) | 63 (20) | 56 (19) |
| ≥ 500 per mm$^3$ - n (%) | 84 (24) | 65 (18) | 64 (18) | 61 (20) | 52 (17) |
| **Virological rebound- events >1000 copies/mL, n(%)** | 60 | 65 | 52 | 66 | 61 |
| Re-suppressed | 37 (62%) | 43 (66%) | 19 (37%) | 35 (53%) | 18 (30%) |
| Remained unsuppressed | 16 (27%) | 6 (9%) | 26 (50%) | 20 (30%) | 29 (48%) |
| No follow up data | 7 (12%) | 16 (25%) | 7 (14%) | 11 (17%) | 14 (23%) |

## 487 48-WEEK OUTCOMES AFTER PROGRAMMATIC TRANSITION TO DOLUTEGRAVIR IN UGANDA

**Suzanne McCluskey**[1], Winnie R. Muyindike[2], Victoria Nanfuka[2], Daniel Omoding[2], Nimusiima Komukama[2], Ian Barigye[2], Lydia Kansiime[2], Justus Tumusiime[2], Ashley Stuckwisch[1], Bethany Hedt-Gauthier[3], Vincent Marconi[4], Mahomed-Yunus Moosa[5], Deenan Pillay[6], Ravindra Gupta[7], Mark Siedner[1]
*[1]Massachusetts General Hospital, Boston, MA, USA, [2]Mbarara University of Science and Technology, Mbarara, Uganda, [3]Harvard Medical School, Boston, MA, USA, [4]Emory University, Atlanta, GA, USA, [5]University of KwaZulu-Natal, Durban, South Africa, [6]University College London, London, UK, [7]Cambridge University, Cambridge, UK*

**Background:** In 2018, Uganda began programmatically switching individuals with HIV-1 RNA <1,000 copies/mL on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART to a fixed-dose regimen of tenofovir/lamivudine/dolutegravir (TLD). Our objective was to estimate the population effectiveness of the TLD transition in public-sector clinics in Uganda.

**Methods:** We conducted a prospective cohort study that enrolled adults ≥18 years who were switched from NNRTI-based first-line ART to TLD at public-sector clinics in Uganda. We observed participants at 3 study visits over 1 year. We obtained blood specimens at each visit and conducted HIV-1 RNA viral load (VL) testing using Cepheid Xpert assays. We fit multivariable logistic regression models to assess predictors of our composite outcome of interest of viral suppression (<50 copies/mL) with retention in care 1 year after switch to TLD.

**Results:** We enrolled 500 participants with a median age of 47 years (IQR 40 – 53); 41% were women. The most common regimen prior to switch was lamivudine/tenofovir/efavirenz (44%), and median duration on ART prior to switch was 8.8 years (IQR 5.7 – 12.2). Over 95% (n=475/499) were virally suppressed (<50 copies/mL) at the time of switch to TLD. The final visit for all participants occurred a median of 54 weeks (IQR 49 – 67) after enrollment, with some participants affected by delays due to COVID-19 mitigation measures. One participant self-elected to disenroll. Only 3% (n=13/499) of participants discontinued TLD due to side effects or clinician discretion. We observed 1% mortality (n=6/499), 2% (n=10/499) lost to follow-up, and 5% (n=23/499) with HIV-1 RNA ≥50 copies/mL at 1 year, with a median VL of 252 copies/mL (IQR 81-78,200 copies/mL). Overall, 92% (n=459/499) were virally suppressed and in care at 1 year. An HIV-1 RNA ≥50 copies/mL at the time of switch to TLD, male gender, and any self-reported ART adherence <90% were all significant negative predictors of the composite outcome of retention in care with a suppressed VL (Table).

**Conclusion:** Rates of viral suppression with retention in care >90% after 1 year on TLD, as well as a 2% TLD discontinuation rate, affirm World Health Organization guidelines for the regional transition to TLD. Nonetheless, an 8% failure rate in HIV-endemic countries corresponds to a large population of individuals. Long-term surveillance of this population, strategies to combat imperfect adherence, and continued attention to treatment options after failure on TLD may be needed.

*[1]Joint Clinical Research Centre, Kampala, Uganda, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Department of State Office of the Global AIDS Coordinator, Washington, DC, USA, [4]Lancet Laboratories, Johannesburg, South Africa, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]Rollins School of Public Health Emory University, Atlanta, USA, [7]The Johns Hopkins University, Baltimore, MD, USA, [8]United States Agency for International Development, Washington, DC, USA, [9]Kenya Medical Research Institute Walter Reed Project Clinical Research Center, Kericho, Kenya, [10]DLH Corporation, Silver Spring, USA, [11]University of Pittsburgh, Pittsburgh, PA, USA, [12]The Johns Hopkins University, Baltimore, MD, USA, [13]Milton Park CRS, Harare, Zimbabwe*

**Background:** Single-tablet tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD) has been rapidly adopted as 1st-line ART for patients initiating treatment and switching from virally-suppressive NNRTI-based 1st regimens in PEPFAR programs. There are limited data, however, on effectiveness and emergence of resistance to TLD in programmatic settings where plasma HIV-1 RNA and drug resistance testing are not used widely.

**Methods:** A prospective observational study is being performed at 13 ACTG sites in six countries (Haiti, Kenya, Malawi, South Africa, Uganda, Zimbabwe) coincident with TLD rollout to assess efficacy and emergence of HIV drug resistance following TLD for 1st, 2nd or 3rd-line ART. This report focuses on the 2 Groups that completed enrollment and 6 months of follow-up: Group 1b (Gp1b) participants on NNRTI-based ART for at least 6 months with HIV-1 RNA ≤1000 cps/mL before switch to TLD; and Group 4 (Gp4) ART-naïve participants initiating 1st-line TLD. The primary objective was to estimate the proportions of participants on TLD with HIV-1 RNA ≤1000 cps/mL and with new DTG resistance mutations at 6 months.

**Results:** From 10/2019-10/2020, we enrolled 600 participants who started TLD: 421 in Gp1b (median age 41years; 80% female) and 179 in Gp4 (median age 35years; 42% female). In Gp1b, median time on ART was 6.6y (IQR 3.3-10.3); 88% were taking EFV with 3TC+TDF or FTC+TDF. In Gp4, median baseline HIV-1 RNA was 4.4 $\log_{10}$ cps/mL (IQR 3.5-5.1). Six participants in Gp1b (1.4%) and 6 in Gp4 (3.4%) discontinued TLD by 6 months, due to withdrawal or loss to follow-up (6 participants), adverse events considered related to TLD (4), and death (2; both Gp4; 1 from TB, 1 unknown cause). Among participants followed on TLD to 6 months, 90% in Gp1b (373/415) and 86% in Gp4 (149/173) had a 6-month HIV-1 RNA result (missing values mainly due to COVID-related virtual visits). HIV-1 RNA ≤1000, <200 and <50 cps/mL was achieved in 99%, 98.4%, and 96% of participants in Gp1b and in 90%, 87.2%, and in 84.6% of Gp4, respectively (Table). A new mutation possibly selected by DTG was observed in 1 participant in Gp1b (T97AT) and none in Gp4.

**Conclusion:** TLD was well tolerated and achieved excellent viral suppression in ART-naïve participants and in participants who switched from virally-suppressive 1st-line ART. An emerging InSTI mutation of uncertain significance was seen in only one participant. These data support early tolerability and efficacy of TLD transition in the public sector.

**Table: Proportion of Participants on TLD at 6 Months with HIV-1 RNA Suppressed to Selected Thresholds: ≤1000, ≤200, and <50 copies/mL**

| | Group 1b* (N=421) | | Group 4** (N=179) | |
|---|---|---|---|---|
| | N/total on TLD with measurement | % (exact 95% CI) | N/total on TLD with measurement | % (exact 95% CI) |
| **Primary virologic outcome:** | | | | |
| HIV-1 RNA ≤1000 copies/mL | 369/373 | 98.9 (97.3, 99.7) | 134/149 | 89.9 (83.9, 94.3) |
| **Exploratory virologic outcomes:** | | | | |
| HIV-1 RNA ≤200 copies/mL | 367/373 | 98.4 (96.5, 99.4) | 130/149 | 87.2 (80.8, 92.1) |
| HIV-1 RNA <50 copies/mL | 358/373 | 96.0 (93.5, 97.7) | 126/149 | 84.6 (77.7, 90.0) |

*Group 1b: participants on NNRTI-based ART for at least 6 months with HIV-1 RNA ≤1000 cps/mL before switch to TLD

**Group 4: ART-naïve participants initiating 1st-line TLD

## 489 WITHDRAWN

## 490 PREDICTORS OF VIRAL SUPPRESSION FOLLOWING ENHANCED ADHERENCE COUNSELING: VISEND TRIAL

**Danielle C. Engamba**[1], C. William Wester[2], Melody M. Mutinta[1], Alepalli P. Kumar[1], Bob Chirwa[1], Getrude Phiri[1], Edford Sinkala[1], Davies Kampamba[3], Mpanji Siwingwa[1], Nyuma Mbewe[1], Aggrey Mweemba[4], Sombo Fwoloshi[1], Andrew Hill[5], Lloyd B. Mulenga[1], Lameck Chirwa[1]

*[1]University Teaching Hospital, Lusaka, Zambia, [2]Vanderbilt University, Nashville, TN, USA, [3]Government of Zambia Ministry of Health, Lusaka, Zambia, [4]Levy Mwanawasa University Teaching Hospital, Lusaka, Zambia, [5]University of Liverpool, Liverpool, UK*

**Background:** The WHO recommends enhanced adherence counseling (EAC) before regimen switch for HIV-positive, antiretroviral therapy (ART)-treated individuals with non-suppressed viral loads (VL). However, there is a paucity of data, especially within a clinical trial setting, on the determinants of viral suppression (VS) following EAC among those failing ART. We thus evaluated predictors of VS among adults failing ART who had undergone EAC in the VISEND clinical trial.

**Methods:** Our trial is a randomized 144 week open label non-inferiority study with adults failing (VL≧ 1000 copies/mL) ART of tenofovir disoproxil fumarate (TDF), lamivudine (3TC) plus efavirenz (EFV) or nevirapine (NVP), switched to 1) TDF,3TC,DTG or 2) tenofovir alafenamide (TAF), emtricitabine (FTC),DTG or 3) lopinavir/ritonavir (LPV/r) or atazanavir/r (ATV/r), zidovudine (ZDV),3TC. Viral

loads and other biomarkers were collected at weeks 12, 24, 48, 72, 96 and 144. Adults with VL≧ 1000 copies/mL at each of these time points underwent EAC involving 3 sessions over a period of 3 months according to existing guidelines. We calculated proportions of individuals who achieved VS post EAC and analyzed factors (demographic and clinical) independently associated with VS post EAC. Using multivariable log regression models, associations were analyzed as crude risk ratios (CRR) and adjusted risk ratios (ARR).

**Results:** The overall VS rates following EAC among individuals with virologic failure was 66%; broken down as follows: TAF,FTC,DTG (78%), TDF,3TC,DTG (71%), ZDV,3TC,ATV/r (62%), and ZDV,3TC,LPV/r (53%). Compared to adults with no formal education, those having primary (ARR 1.55 [1.32–1.81], P<0.001) or secondary level education (ARR 1.93 [1.65 – 2.27], P<0.001) were more likely to achieve VS. Those less likely to suppress post EAC were individuals on ART for > 5 years (ARR 0.75 [ 0.75–0.75], P<0.001), VL > 10,000 copies/mL at time of failure (0.48 [0.48 – 0.48], P<0.001), presence of comorbidities (ARR 0.77 [0.66 – 0.90], P=0.001) and those taking concomitant medications (ARR 0.67 [0.58-0.79], P<0.001). Having suffered from COVID-19 infection had no association with VS post EAC (ARR 0.59 [0.22–1.58], P=0.30). Consistent results are in Table 1.

**Conclusion:** In the VISEND trial, EAC led to VS rates near the WHO target of 70% with disparities in outcomes according to gender, education, and other factors. There is a need to routinely incorporate EAC into clinical trials and practice before regimen switch in order to maximize outcomes.

**Table 1**: Predictors of Viral Suppression after enhanced adherence counselling

| Variable | CRR (95% CI) | ARR (95% CI) | *p*-value |
|---|---|---|---|
| **Sex** | | | |
| Male | 1 | 1 | |
| Female | 1.48 [1.05 – 2.09] * | 3.49 [2.17 – 5.62] | <0.001 |
| **Age** | | | |
| 18 – 24 | 1 | - | |
| 25 – 34 | 1.75 [0.73– 4.17] | - | |
| 35 – 59 | 2.14 [0.95 – 4.85] | - | |
| ≥ 60 | 2.0 [0.65 – 6.20] | - | |
| **Educational level** | | | |
| No formal education | 1 | 1 | |
| Primary | 1.48 [0.55 – 4.04] | 1.55 [1.32 – 1.81] | <0.001 |
| Secondary | 1.16 [0.42 – 3.18] | 1.93 [1.65 – 2.27] | <0.001 |
| Tertiary | 1.27 [0.43 – 3.74] | | |
| **Duration on ART (years)** | | | |
| < 2 | 1 | 1 | |
| 2 – 4 | 0.67 [0.53 – 0.86] * | - | |
| ≥ 5 | 0.60 [0.51 – 0.72] * | 0.75 [0.75 – 0.75] | <0.001 |
| **First viral load (copies/mL)** | | | |
| 1,000 – 5,000 | 1 | 1 | |
| 5,001 – 10,000 | 0.84 [0.42 – 1.69] | 1.50 [1.09 – 2.05] | 0.013 |
| >10,000 | 0.61 [0.38 – 0.97] * | 0.48 [0.48 – 0.48] | <0.001 |
| **Baseline CD4 cell count (cells/mm³)** | | | |
| < 200 | 1 | 1 | |
| 200 – 499 | 0.99 [0.65 – 1.52] | 0.43 [0.37 – 0.50] | <0.001 |
| ≥ 500 | 0.78 [0.36 – 1.70] | 0.11 [0.02 – 0.68] | 0.017 |
| **SARS-CoV-2 status (PCR results)** | | | |
| Negative | 1 | 1 | |
| Positive | 0.67 [0.32 – 1.42] | 0.59 [0.22 – 1.58] | 0.295 |
| **Concomitant Medications** | | | |
| No | 1 | 1 | |
| Yes | 0.74 [0.56 – 0.96] | 0.67 [0.58 0.79] | <0.001 |
| **Comorbidities** | | | |
| No | 1 | 1 | |
| Yes | 1.01 [0.73 – 1.40] | 0.77 [0.66 – 0.90] | 0.001 |

## 491 LONG-ACTING LENACAPAVIR IN PEOPLE WITH MULTIDRUG RESISTANT HIV-1: WEEK 52 RESULTS

**Onyema Ogbuagu**[1], Sorana Segal-Maurer[2], Cynthia Brinson[3], Ploenchan Chetchotisakd[4], Kenneth Lichtenstein[5], Joseph McGowan[6], Andrew A. Wiznia[7], Kimberly Workowski[8], Hui Wang[9], Nicolas Margot[9], Hadas Dvory-Sobol[9], Martin Rhee[9], Jared Baeten[9], Jean-Michel Molina[10]

*[1]Yale University, New Haven, CT, USA, [2]New York Presbyterian Hospital, New York, NY, USA, [3]Central Texas Clinical Research, Austin, TX, USA, [4]Srinagarind Hospital, Khon Kaen, Thailand, [5]Eisenhower Medical Center, Palm Springs, CA, USA, [6]AbbVie, Inc, North Chicago, IL, USA, [7]Bronx Municipal Hospital Center, Bronx, NY, USA, [8]Emory University, Atlanta, GA, USA, [9]Gilead Sciences, Inc, Foster City, CA, USA, [10]Hôpital Saint-Louis, Paris, France*

**Background:** Lenacapavir (LEN), a potent first-in-class inhibitor of HIV-1 capsid function, is in development for treatment and prevention of HIV-1 infection. CAPELLA is an ongoing, Phase II/III study in heavily treatment-experienced (HTE) people with HIV-1 (PWH) with multidrug-resistance and ongoing viremia (≥ 400 copies/mL) evaluating LEN in combination with an optimized background regimen (OBR).

**Methods:** In the randomized cohort (Cohort 1), participants were assigned (2:1) to add oral LEN or placebo to their failing regimen (600 mg on Day 1[D] and 2 and 300 mg on D8). At D15, those on oral LEN received subcutaneous (SC) LEN 927 mg every 6 months; those on placebo started the 2-week oral lead-in, followed by SC Q6M. All randomized participants initiated an investigator-selected, OBR at D15. In the non-randomized cohort (Cohort 2), participants started OBR concurrent with LEN (oral lead-in → SC). We report the secondary endpoint of W52 efficacy by FDA-snapshot algorithm in the randomized cohort and additional available efficacy and safety from both cohorts.

**Results:** 72 participants were enrolled: 36 in each cohort. Overall, 25% were female, 38% Black, median age 52 years, 19% had VL > 100k c/mL, 64% had CD4 <200 cells/μL, 46% had HIV-1 resistant to all 4 major classes (NRTI, NNRTI, PI, InSTI), and 17% did not have any fully active agents in the OBR. In Cohorts 1 and 2 at W26, 81% (29/36) and 81% (29/36) achieved VL<50 c/mL. At W52, in Cohort 1, 83% (30/36) had VL< 50 c/mL; most in Cohort 2 have not reached W52 yet. At W52, CD4 count increased by a median 83 cells/μL (Q1 to Q3: 21 to 142, n=41). Eight participants had emergent LEN resistance (4 in Cohort 1 and 4 in Cohort 2); other than 1 who died at W11 (previously reported), all 7 either had evidence of poor adherence to the OBR (n=4) or did not have any fully active agents in the OBR (n=3).No participant experienced a study drug-related serious adverse event. One participant discontinued LEN at W52 due to an AE of Grade 1 injection site nodule. LEN-related injection site reactions (ISRs) occurred in 63% (45/72) and were mostly mild or moderate (43/45). The most common non-ISR AEs were nausea and diarrhea (13% each) and COVID-19 (11%).

**Conclusion:** Subcutaneous LEN in combination with OBR led to high rates of virologic suppression and immunologic recovery in HTE PWH at one year and was well tolerated. These results support the ongoing evaluation of LEN for treatment of multi-drug resistant HIV-1 infection.

## 492 FEASIBILITY AND VIRAL RESPONSE TO TREATING ACUTE/EARLY HIV IN A MULTINATIONAL STUDY

**Eric S. Daar**[1], Justin Ritz[2], Lu Zheng[2], Jintanat Ananworanich[3], Cecelia Kanyama[4], Susan J. Little[5], Susan E. Cohn[6], Sharon A. Riddler[7], Ann C. Collier[8], Robert Coombs[8], Lawrence Fox[9], Javier R. Lama[10], Trevor A. Crowell[11]

*[1]Harbor–UCLA Medical Center, Torrance, CA, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University of Amsterdam, Amsterdam, Netherlands, [4]University of North Carolina Project, Lilongwe, Malawi, [5]University of California San Diego, La Jolla, CA, USA, [6]Northwestern University, Chicago, IL, USA, [7]University of Pittsburgh, Pittsburgh, PA, USA, [8]University of Washington, Seattle, WA, USA, [9]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [10]Asociacion Civil Impacta Salud y Educacion, Lima, Peru, [11]US Military HIV Research Program, Silver Spring, MD, USA*

**Background:** Antiretroviral therapy (ART) initiated during acute and early HIV infection (AEHI) may limit reservoir size and facilitate post-ART control. ACTG A5354 is a prospective study designed to assess virologic and immunologic impact of ART during different stages of AEHI. We report the feasibility to rapidly identify, start ART and achieve viral suppression during AEHI in a multinational study.

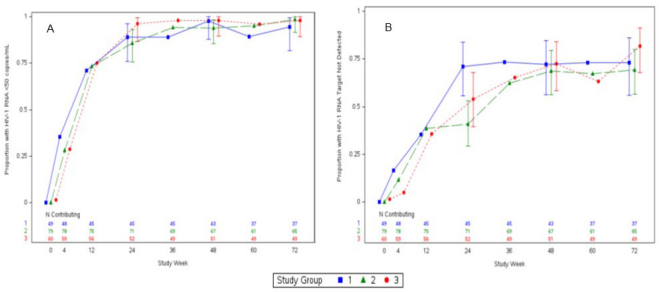
**Methods:** A5354 enrolled adults with AEHI at 30 sites in the Americas, Africa, and Southeast Asia. Participants were encouraged to start ART at presentation with suspected AEHI. Fiebig stage at ART initiation was retroactively assigned by centralized testing; categorized as Group 1 (Fiebig I/II), Group 2 (Fiebig III/IV) or Group 3 (Fiebig V).

**Results:** From Jan 2017 to Dec 2019, 195 participants with suspected Fiebig I-V were enrolled and initiated ART. Three were found to not have HIV and four were Fiebig VI, and therefore not followed. Of 188 followed, 132 (70%) were from US and 56 (30%) from international sites. Fiebig stages I (n=6), II (n=43), III (n=56), IV (n=23), and V (n=60) with 72% screened and initiated treatment on same day. Integrase inhibitor-based ART was started by 98%. Enrollment characteristics were similar across Groups 1-3 (G1-3) with median age 27 (IQR 23, 38) years, 14% female, 96% cisgender, 54% African American/Black, 35% Hispanic with 36% hospitalized and 28% asymptomatic. Median (IQR) plasma HIV RNA in G1-3 were 6.4 (5.3, 7.0), 6.5 (6.0, 7.0) and 5.4 (5.0, 6.4) $\log_{10}$ copies/mL, respectively. Median (IQR) CD4 (cells/$mm_3$) for G1-3 were 348 (211, 493), 383 (264, 507) and 490 (366, 652), respectively. Premature study discontinuation occurred in 16% of US and 17% of international participants. Over 72 weeks of follow-up, ART was held or switched in 34 (18%) participants and viral failure occurred in 4 (2%). Time to HIV RNA <50 copies/mL was similar across groups, but G1 was faster to RNA target not detected than G2 and G3, despite similar baseline HIV RNA (Figure).

**Conclusion:** Rapid ART initiation was feasible, well-tolerated, and virologically effective in a prospective, multinational study of AEHI. Shortened time to HIV RNA target not detected after ART initiation during seronegative phase may suggest virologic benefits. This data demonstrates ability to conduct global projects designed to rapidly treat AEHI, as well as potential beneficial virologic

effects of early ART. Additional analyses will assess impact of this strategy on viral reservoir and host immune responses.

**Figure. Proportion (95% CI) of participants with plasma HIV RNA <50 copies/mL (A) and RNA target not detected (B) over time**



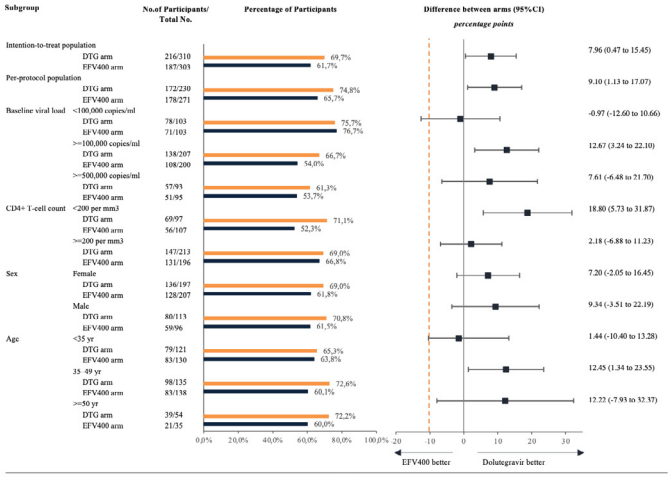




**Figure 1** Efficacy on the viral load (<50 copies/mL) according to subgroups at 192-week

## 493 LONG-TERM OUTCOMES OF DOLUTEGRAVIR AND EFAVIRENZ-400 AS FIRST-LINE ART IN CAMEROON

**Mireille Mpoudi Ngole-Etame**[1], Tamara Tovar Sánchez[2], Pierrette Omgba-Basega[3], Justin Désiré Olinga[4], Eric Mimbe[4], Michel Foalem[5], Raphaël Pelloquin[2], Marie Varloteaux[4], Marcel Tongo[6], Martine Peeters[2], Jacques Reynes[7], Alexandra L. Calmy[8], Eric Delaporte[2], Charles Kouanfack[9]

*[1]Military Hospital Region N°1, Yaoundé, Cameroon, [2]TransVIHMI, University of Montpellier–IRD–INSERM, Montpellier, France, [3]Cité Verte District Hospital, Yaoundé, Cameroon, [4]Cameroon ANRS-site, Yaoundé, Cameroon, [5]Yaoundé Central Hospital, Yaoundé, Cameroon, [6]Center of Research for Emerging and Re-Emerging Diseases, Yaoundé, Cameroon, [7]Montpellier University Hospital Cente, Montpellier, France, [8]Geneva University Hospitals, Geneva, Switzerland, [9]Faculty of Medicine and Pharmaceutical Sciences University of Dschang, Dschang, Cameroon*

**Background:** WHO recommends dolutegravir 50mg (DTG) as first-line antiretroviral treatment (ART) and efavirenz 400mg (EFV400) as second option since 2019. Both ART efficacy and safety in real living conditions in low- and middle-income countries (LMIC) were previously demonstrated by the NAMSAL study group and provided solid elements for these recommendations. Nevertheless, only after three years of follow-up the remarkable efficacy in favor of DTG is shown. Here we present data of the fourth year of follow-up.

**Methods:** NAMSAL was an open-label, multicenter, randomized, Phase III non inferiority trial conducted in Cameroon over 96-week, extended as post-trial follow-up as a prospective cohort until 192-week. HIV-1 infected ARV-naive adults with HIV-RNA viral load (VL)>1000 copies/mL were randomized and maintained in the base arm (1-DTG:1-EFV), both combined with tenofovir-disoproxil-fumarate (TDF)/lamivudine (3TC). The primary end point was the proportion of participants with a VL of less than 50 copies/mL at week 48; secondary outcomes were assessed with superiority-test.

**Results:** At week 192, a higher proportion of the DTG group (69%, 214/310) achieved a VL < 50 copies/mL than did of the EFV400 group (62%, 187/303; difference, 7.3%; CI-95%, [0.20;15.45], p-value=0.057; Figure 1). Per-protocol results were close to ITT, 75% (DTG: 172/230) and 66% (EFV400: 178/271) respectively (difference, 7.9%; CI-95%, [0.3;16.27], p-value=0.035). During the fourth-year of follow-up, five (DTG: 2; EFV400: 3) new virological failures (WHO-definition) without related resistance mutations (NNRTI+/-NRTI) were observed. 24 new severe adverse-events (SAE) were observed (DTG: 13, EFV400: 11). Over four years mean weight gain was more important in women compared to men (Women: DTG +8.0 Kg, EFV400 +5.0 Kg, p-value=0.010; Men: DTG +6.0 Kg, EFV400 +4.0 Kg, p-value=0.024). Incidence of obesity in women was 17% and 11% (p=0.140) respectively, in men 26% and 3% (p<0.001) respectively.

**Conclusion:** Fourth-year of follow-up of HIV-1 infected ARV-naive adults in LMIC, who started on DTG-based and low-dose EFV-based regimen, suggested superiority of DTG based regimen; low EFV-related and no DTG-related resistance mutations rates were observed. However, weight gain tendency is important among women on DTG, a close cardiovascular and metabolic monitoring should be recommended to take into account risks related to weight-gain.

## 494 B/F/TAF FIVE-YEAR OUTCOMES IN TREATMENT-NAÏVE ADULTS

**David A. Wohl**[1], Anton Pozniak[2], Kimberly Workowski[3], Debbie Hagins[4], Eric S. Daar[5], Chloe L. Orkin[6], Ellen Koenig[7], Karam Mounzer[8], Samir Gupta[9], Hailin Huang[10], Rima K. Acosta[10], Jason Hindman[10], Jared Baeten[10], Hal Martin[10], Paul E. Sax1[1]

*[1]University of North Carolina School of Medicine, Chapel Hill, NC, USA, [2]Chelsea and Westminster Hospital, London, UK, [3]Emory University, Atlanta, GA, USA, [4]Chatham County Health Department, Savannah, GA, USA, [5]Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA, USA, [6]Barts Health NHS Trust, Royal London Hospital, Ambrose King Centre, London, UK, [7]Instituto Dominicano de Estudios Virólgicos, Santo Domingo, Dominican Republic, [8]Philadelphia FIGHT Community Health Centers, Philadelphia, PA, USA, [9]Indiana University School of Medicine, Indianapolis, IN, USA, [10]Gilead Sciences, Inc, Foster City, CA, USA, [11]Brigham and Women's Hospital, Boston, MA, USA*

**Background:** Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a guidelines-recommended single-tablet regimen for people with HIV-1 (PWH). We present 5-year cumulative outcomes of two Phase III studies of B/F/TAF in treatment-naïve PWH.

**Methods:** We conducted 2 randomized, double-blind, Phase III studies of B/F/TAF in treatment-naïve adults – Study 1489 (1489): B/F/TAF vs DTG/ABC/3TC and Study 1490 (1490): B/F/TAF vs DTG+F/TAF. After completing 144W of blinded treatment, participants were offered continuation of B/F/TAF for 96W in open-label extensions (OLEs). Efficacy was assessed as proportion with HIV-1 RNA <50 copies/mL at each visit after starting B/F/TAF using missing=excluded analysis; safety by adverse events (AEs) and laboratory results. Bone mineral density (BMD) was measured in those randomized to B/F/TAF in 1489. We present cumulative results for participants treated with B/F/TAF in randomized and/or OLE phases through a maximum of 240W of follow up.

**Results:** 314 participants in 1489 and 320 in 1490 randomized to B/F/TAF with 252 and 254 enrolled in OLE, respectively. 315 randomized to DTG/ABC/3TC in 1489 and 325 randomized to DTG+F/TAF in 1490 and 254 and 265 enrolled in OLE, respectively. Baseline (BL) demographics of B/F/TAF participants in 1489 and 1490 include: median age 31 and 33, 9% and 13% female, 37% and 30% Black/African descent, and 23% and 26% Latino/Hispanic, respectively. Efficacy was >98% after W48 at each study visit through W240 in both studies. No resistance to components of B/F/TAF was detected in the resistance analysis population. During the OLE, 6/504 B/F/TAF participants experienced an AE that led to drug discontinuation, none were renal; ≤1.6% had a Grade 3 or 4 drug-related AE. Among B/F/TAF participants through W240, median changes in eGFR: -8.2 mL/min (1489) and -8.5 mL/min (1490), median change in TC:HDL ratio: 0 (1489) and 0.1 (1490). Median change in weight from BL to W240 was 6.1kg in B/F/TAF participants; median weight change for comparators at W144: 3.5kg (1489) and 5.0kg (1490), with 2.4kg and 1.3kg additional gains observed between W144 to W240, respectively. Mean % changes (SD) in hip and spine BMD through W240 in B/F/TAF participants were -0.29% (5.29) and -0.23% (5.16), respectively.

**Conclusion:** Over 5 years of follow up in treatment-naïve persons living with HIV, B/F/TAF was well tolerated and highly efficacious. These results confirm long term safety and efficacy of B/F/TAF.

## 495 HIV-1 RNA DECAY IN SEMEN AND RECTUM WITH DTG PLUS 3TC VERSUS BIC/FTC/TAF

**Arkaitz Imaz**[1], Sofia Scevola[1], Jordi Niubo[1], Pere Domingo[2], Guillermo Verdejo[3], Adrià Curran[4], Vicens Diaz de Brito[5], Juan M. Tiraboschi[1], Sandra Morenilla[1], Benito Garcia-Vidal[1], Irene Soriano[1], Daniel Podzamczer[1]
*[1]Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain, [2]Hospital de Sant Pau, Barcelona, Spain, [3]Hospital Sant Camil, Sant Pere de Ribes, Spain, [4]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [5]Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain*

**Background:** The assessment of HIV decay kinetics in genital fluids and rectum may assist in predicting the potential risk of sexual transmission after initiating antiretroviral therapy (ART). HIV decay in semen and rectum have not yet been described for the dual combination dolutegravir (DTG) plus lamivudine (3TC).
**Methods:** Open-label, multicenter, randomized, pilot clinical trial. Inclusion criteria were: ART–naive males with plasma HIV-1 RNA <500,000 copies/mL, CD4 cell count >200/µL, negative for HBV and absence of mutations associated with resistance to the study treatments at screening. Patients with acute HIV infection were excluded. Participants were randomized 2:1 to initiate first-line ART with DTG 50 mg plus 3TC 300 mg OD or BIC/F/TAF 50/200/25 mg OD, respectively, and randomization was stratified by plasma HIV-1 RNA below or above 100,000 copies/mL and CD4 count below or above 350 cells/ µL. HIV-1 RNA was measured in blood plasma (BP), seminal plasma (SP) and rectal fluid (RF) at baseline (BL), days 3, 7, 14 and 28, and weeks 12 and 24 (quantification limit: 20 copies per mL or per swab in case of RF). The McNemar's test and the Chi-Square (or Fisher exact test) were used to compare continuous or categorical variables, respectively.
**Results:** 24 participants were included (16 in the DTG+3TC arm and 8 in the BIC/FTC/TAF arm). Median (range) BL characteristics were: age 31 (20-60) years; CD4 count 398 (216-716) cells/µL; HIV-1 RNA in BP 4.56 (3.09-5.65) $log_{10}$ copies per mL; HIV-1 RNA in SP 2.38 (1.30-5.06) $log_{10}$ copies per mL; and HIV-1 RNA in RF 3.2 (1.30-4.36) $log_{10}$ copies per swab. No statistically significant differences were observed between treatment groups in HIV-1 RNA decline from BL, as well as in the percentage of individuals with HIV-1 RNA <20 copies per mL (or swab) in BP, SP and RF at each study timepoint. Undetectable viral load was achieved more rapidly in SP and RF compared to BP in both groups. At Day 28, 81% (13/16) and 87% (7/8) of individuals receiving DTG+3TC and BIC/FTC/TAF, respectively, had HIV-1 RNA <20 copies per mL (or swab) in both SP (p >0.999) and RF (p >0.999), while the viral suppression rate in BP was 56% and 75%, respectively (p=0.657). At week 12 and week 24 most subjects had HIV-1 RNA <20 copies per mL (or swab) in BP, SP and RF (Table 1).
**Conclusion:** Both DTG+3TC and BIC/F/TAF achieved rapid HIV-1 RNA suppression in SP and RF and no significant differences were observed between treatment groups in all study timepoints from BL through week 24.

**Table 1**

| Compartment | Treatment Group | Individuals with HIV-1 RNA <20 copies per mL (or swab in case of RF) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Baseline | Day 3 | Day 7 | Day 14 | Day 28 | Week 12 | Week 24 |
| Blood Plasma | DTG+3TC (n=16) | 0 | 0 | 0 | 5 (31%) | 9 (56%) | 14 (87%) | 15 (94%) |
| | BIC/FTC/TAF (n=8) | 0 | 0 | 1 (12%) | 2 (17%) | 6 (75%) | 7 (87%) | 7 (87%) |
| | *P value** | - | - | *0.333* | *>0.999* | *0.657* | *>0.999* | *>0.999* |
| Semen | DTG+3TC (n=16) | 6 (37%) | 6 (37%) | 11 (69%) | 14 (87%) | 13 (81%) | 15 (94%) | 14 (87%) |
| | BIC/FTC/TAF (n=8) | 3 (37%) | 4 (50%) | 6 (75%) | 7 (87%) | 7 (87%) | 8 (100% | 8 (100%) |
| | *P value** | *0. 675* | *0.673* | *>0.999* | *>0.999* | *>0.999* | *>0.999* | *0.536* |
| Rectal Fluid | DTG+3TC (n=16) | 1 (6%) | 6 (37%) | 6 (37%) | 10 (62%) | 13 (81%) | 15 (94%) | 16 (100%) |
| | BIC/FTC/TAF (n=8) | 0 | 1 (12%) | 4 (50%) | 4 (50%) | 7 (87%) | 8 (100%) | 7 (87%) |
| | *P value** | *>0.999* | *0.352* | *0.673* | *0.673* | *>0.999* | *>0.999* | *0.333* |

*DTG+3TC vs BIC/FTC/TAF

## 496 ANTIRETROVIRAL THERAPY ADHERENCE IN MEDICARE FEE-FOR-SERVICE BENEFICIARIES WITH HIV

**Pengxiang Li**[1], Girish Prajapati[2], Zhi Geng[1], Vrushabh P. Ladage[3], Jean M. Arduino[2], Dovie L. Watson[1], Robert Gross[1], Jalpa A. Doshi[1]
*[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Merck & Co, Inc, Kenilworth, NJ, USA, [3]Dartmouth College, Hanover, NH, USA*

**Background:** Medicare has emerged as a major source of HIV care for people living with HIV (PLWH) in the U.S. Yet little is known about antiretroviral therapy (ART) adherence among PLWH in the Medicare program. This study aimed to assess factors associated with poor adherence to ART and describe healthcare resource use (HCRU) and costs by adherence levels among PLWH in Medicare program.
**Methods:** A retrospective analyses of 2013-2018 100% Medicare fee-for-service claims was conducted to examine 12-month adherence among PLWH initiating a new (index) anchor ART agent (InSTI, NNRTI, or PI class). Adherence to any anchor ART agent was measured using the proportion of days covered (PDC) method (days spent in hospital were not counted in calculating PDC). Patients were categorized into 3 groups: PDC≥0.95, 0.95>PDC≥0.70, and PDC<0.70. Multinomial logistic regression assessed factors associated with different adherence levels. All-cause and HIV-related 12-month HCRU and costs were examined by adherence groups.
**Results:** The final study sample included 48,627 PLWH: 17% with PDC<0.70, 30% with PDC≥0.70 but <0.95, and 53% with PDC≥0.95. Differences in characteristics were observed across the 3 groups (Table). Multivariable regressions showed that younger age, female sex, Black race, Hispanic ethnicity, full low-income subsidy status, higher comorbidity score, index anchor agent from PI class, and conditions such as mental illnesses and substance use were associated with higher odds of being in the lower adherence groups relative to the PDC≥0.95 group (p <0.05 for all). All-cause hospitalization rates were higher among lower adherence groups (PDC<0.70: 33%; 0.95>PDC≥.70: 25%; PDC≥0.95: 21%, p<0.05). All-cause total costs were lower among lower adherence groups (PDC<0.70: $42,690; 0.95>PDC≥0.70: $59,352; PDC≥0.95: $64,877, p<0.05), largely driven by lower pharmacy costs (PDC<0.70: $21,921; 0.95>PDC≥0.70: $42,584; PDC≥0.95: $50,695, p<0.05). However, medical costs were higher among lower adherence groups (PDC<0.70: $20,769; 0.95>PDC≥0.70: $16,768; PDC≥0.95: $14,182, p<0.05). Similar patterns were observed with HIV-related HCRU and costs.
**Conclusion:** Among Medicare beneficiaries living with HIV, poor adherence to anchor ART was commonly observed. Patients with lower adherence had higher hospitalization rates and medical costs. The study findings provide insights into the characteristics of patients with poor ART adherence and highlights the need for interventions to mitigate barriers to adherence in PLWH in Medicare.

Table. Selected sample characteristics by level of adherence to any anchor ART over 12-months of follow-up from initiation of new anchor ART agent among PLWH in Medicare

| Characteristics | Overall (n=48,627) | PDC ≥ 0.95 (n=25,760) | 0.95 > PDC ≤ 0.70 (n=14,696)* | PDC < 0.70 (n=8,171)* |
|---|---|---|---|---|
| Age, mean (SD) | 54.5 (10.9) | 56.2 (10.4) | 53.8 (10.8) | 50.2 (11.4) |
| Female, n (%) | 12463 (25.6) | 5969 (23.2) | 3928 (26.7) | 2566 (31.4) |
| White, n (%) | 23079 (47.5) | 13761 (53.4) | 6456 (43.9) | 2862 (35.0) |
| Black, n (%) | 21052 (43.3) | 9508 (36.9) | 6918 (47.1) | 4626 (56.6) |
| Hispanic,** n (%) | 3044 (6.3) | 1639 (6.4) | 935 (6.4) | 470 (5.8) |
| Other, n (%) | 1452 (3.0) | 852 (3.3) | 387 (2.6) | 213 (2.6) |
| Full low-income subsidy, n (%) | 39944 (82.1) | 20420 (79.3) | 12322 (83.8) | 7202 (88.1) |
| Index Anchor Agent: INSTI, n (%) | 32751 (67.4) | 18011 (69.9) | 9819 (66.8) | 4921 (60.2) |
| Index Anchor Agent: NNRTI, n (%) | 7842 (16.1) | 4124 (16.0) | 2389 (16.3) | 1329 (16.3) |
| Index Anchor Agent: PI, n (%) | 8034 (16.5) | 3625 (14.1) | 2488 (16.9) | 1921 (23.5) |

*Both groups were significantly different from PDC≥0.95 group at p<0.05 on age, sex, race/ethinicity, low-income subsdity status, and index anchor agent class. ** May be underreported since one single field captures both race and ethnicity in Medicare administrative data. Abbreviations: ART: antiretroviral therapy; PDC: Proportion of Days Covered; INSTI: Integrase Strand Transfer Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor

## 497 LOW-LEVEL VIREMIA AND VIROLOGICAL FAILURE IN HIV ANTIRETROVIRAL THERAPY

**An Jing**[1], Lao Yunfei[1], Tang Songyuan[2], Dong Xingqi[1], Lou Jingcheng[1], Li Tianshu[1]
*[1]Yunnan Provincial Infectious Disease Hospital, Kunming, China, [2]Kunming Medical University, Kunming, China*

**Background:** HIV plasma viral load (pVL) is an important indicator to monitor treatment response in combination antiretroviral therapy (cART). During cART course, patients may experience small increases in pVL, namely 50 to 999 copies/mL, not reaching the threshold for viral failure (≥1000 copies/mL) based on China guideline, known as low-level viraemia (LLV). However, the overall impact of LLV on clinical outcomes remains largely unknown. The objective of this study was to investigate the long-term impact of LLV on virological failure in patients receiving cART.
**Methods:** We analyzed ART-naive adults from the cohort of Yunnan (China) initiating cART from 2004 to 2018. LLV was defined as the occurrence of at least one time of plasma viral load measurement of 51–999 copies per mL during cART. Instances of LLV were grouped in ranges of 51–199, 200–399 and 400–999 copies per mL. Patients with multiple instances of LLV were classified in the range of their highest results. Multivariable Cox models were used to estimate the association of LLV with virological failure.
**Results:** A total of 76,736 patients were included. The median age was 37 years (IQR, 30–44 years), 63.6% were male, median baseline CD4+ T count

was 247 (176–411) cells per milliliter. Median follow-up length was 184 weeks (IQR 94-305weeks). LLV occurred in17,832 (23.2%) patients. Virological failure (one or more viral load measurement of ≥1000 copies per mL) occurred in 12,850(16.7%) patients. Patients with LLV499-999 showed the highest rate of virological failure (4.12; 95% CI: 3.86 to 4.38) compared with patients in the LLV50-199 (1.77; 95% CI: 1.67 to 1.88), LLV200-399 (2.79; 95% CI: 2.56 to 3.03) and no LLV (1.82; 95% CI: 1.76 to 1.88) groups, respectively. After excluding 6,405 patients with initial virological failure, 12,779 patients with only one viral load result, and 694 patients with less than 1 year of follow-up on ART, the rest 56,858 patients were adopted for cox proportional hazards analysis. Adjusted HRs increased with increasing range of LLV. LLV200-399 and LLV400-999 was strongly associated with virological failure (aHR, 1.39; 95% CI: 1.27 to 1.53) and (aHR, 2.02; 95% CI: 1.87 to 2.18).
**Conclusion:** In Yunnan cohort, LLV200-399 and LLV 400–999 were strongly associated with the virological failure of viral load measurement ≥1000 copies per mL. Management of low-level viraemia and re-identification of viral failure in China cART guideline should be considered.

### 498 DURABLE HUMAN HIV-SPECIFIC bNAb PRODUCTION 3 YEARS AFTER AAV8-MEDIATED GENE TRANSFER

**Joseph P. Casazza**[1], Evan M. Cale[1], Sandeep Narpala[1], Laura Novik[1], Galina V. Yamshchikov[1], Bob C. Lin[1], Janardan P. Pandey[2], Adrian McDermott[1], Mario R. Roederer[1], Alejandro Balazs[3], David Baltimore[4], Richard A. Koup[1], Julie E. Ledgerwood[1], John R. Mascola[1]
*[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [2]Medical University of South Carolina, Charleston, SC, USA, [3]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [4]Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA, USA*

**Background:** Gene transfer protocols offer an alternative to repeated injections of bNAbs as a means of maintaining effective immunoprophylaxis. VRC07 is a bNAb targeting the CD4 binding site of the HIV-1 envelope glycoprotein.
**Methods:** Ten HIV-infected volunteers on effective ARV therapy were enrolled in a phase I dose escalation trial of an AAV8 vectored VRC07 gene transfer at doses of 5x1010 (N=3), 5x1011 (N=3), and 2.5x1012 (N=4) viral genomes per kilogram (vg/kg) given by IM injection. Volunteers were between ages 22 and 60 years at enrollment and have been followed for 3 months - 3.75 years.
**Results:** Product administration was well tolerated. No product related serious events occurred during this time. Vector-based VRC07 production was found in serum from all volunteers given AAV8-VRC07. Data from the long-term follow-up of 8 individuals followed for 1-1.5 years suggest a characteristic pattern of bNAb production defined by an early peak in VRC07 concentration 4-6 weeks after product administration, a decrease in VRC07 concentration from 7-14 weeks after product administration and then a slow increase in VRC07 concentration from 16 weeks onward resulting in stable or continually increasing Ab concentration. In 3 of the 8 individuals the secondary increase in VRC07 was either blunted or eliminated by a product-induced non-idiotypic anti-drug antibody (ADA) response. In the 5 individuals without significant ADA, peak VRC07 concentrations were 0.15-0.48 µg/ml in the 5x1010 dose group, 0.59 µg/ml in the 5x1011 dose group and 1.2-3.1 µg/ml in the 2.5x1012 dose group. At 1.5 years after product administration VRC07 concentration were 0.34-0.48 µg/ml in the 5x1010 dose group, 0.45 µg/ml in the 5x1011 dose group and 0.31-3.1 µg/ml in the 2.5x1012 dose group. Data from the low dose group show stable VRC07 expression through 2.5-3 years after product administration. After protein A IgG purification, IgG containing VRC07 was characterized in the 7 individuals. Pseudovirus neutralization $IC_{80}$s for 5 tier 2 pseudovirus for in vivo and ex vivo produced VRC07 were similar.
**Conclusion:** These data suggest that adeno-associated viral vectors can safely be used to stably produce biologically active bNAbs in the majority of humans given product for over a 1.5 year period. AAV8 mediated gene transfer may offer a means to generate effective immunoprophylaxis. Identifying the cause of the ADA response may allow further increases in bNAb concentrations.

### 499 MECHANISMS OF HOPEAPHENOL INHIBITION OF HIV PROVIRUS FOLLOWING DISCONTINUATION

**Ian Tietjen**[1], Amanda Sciorillo[1], Maya E. Naidu[2], Cole Schonhofer[2], Zahra Haq[2], Toshitha Kannan[1], Andrew Kossenkov[1], Karam Mounzer[3], Colin Hart[1], Kwasi Gyampoh[1], Zhe Yuan[1], Karren D. Beattie[4], Topul Rali[5], Rohan A. Davis[4], Luis J. Montaner[1]
*[1]Wistar Institute, Philadelphia, PA, USA, [2]Simon Fraser University, Burnaby, Canada, [3]Philadelphia FIGHT, Philadelphia, PA, USA, [4]Griffith University, Brisbane, Australia, [5]University of Papua New Guinea, Port Moresby, Papua New Guinea*

**Background:** People living with HIV (PLWH) on suppressive ART continue to harbor transcriptionally-active virus, which can lead to ongoing viral antigen production, long-term inflammation, and increased risk of age-related co-morbidities. Compounds that block viral transcription from infected CD4+ T-cells may help reduce co-morbidity risks arising from ongoing immune activation due to chronic viral antigens.
**Methods:** J-Lat 10.6 cells containing a latent, GFP-tagged HIV provirus were monitored for HIV expression by flow cytometry. Peripheral blood mononuclear cells (PBMC) were obtained from 4 donors, infected in vitro with HIV-1NL4.3 ± hopeaphenol, and assessed for p24Gag viral antigen after 6 d. Transcriptome changes were monitored with RNAseq and Ingenuity Pathway Analysis software. Effects of hopeaphenol on HIV long-terminal repeat-driven reporter expression were tested in transfected HEK-293T cells. CDK9 enzymatic activity was determined with a commercial kit. CD4+ T-cells from 3 PLWH were treated ± hopeaphenol for 24 h, extensively washed and rested for 24 h, and stimulated with anti-CD3/CD28 beads for 24 h, and supernatant viral RNA was measured by qRT-PCR. Group differences were analyzed by two-sided, paired t-test.
**Results:** Hopeaphenol inhibited PMA-stimulated viral transcription in J-Lat 10.6 cells ($EC_{50} = 2.5 \pm 1.9$ µM) and HIV replication in PBMC ($EC_{50} = 0.98 \pm 0.41$ µM) without cytotoxicity. RNA sequencing of PMA-treated J-Lat 10.6 cells ± 10 µM hopeaphenol identified downregulation of protein kinase C activation (but not TNFα) of HIV and host transcripts involved in NF-κB signaling. Hopeaphenol also inhibited both cellular NF-κB-driven reporter expression induced by PMA ($EC_{50}$s = 9.0 ± 2.3 µM) but not TNFα ($EC_{50} > 30$ µM) and CDK9 (but not CK2) enzymatic activity ($EC_{50} = 0.11 \pm 0.07$ µM). Notably, when J-Lat 10.6 cells were pre-treated with 3 µM hopeaphenol and extensively washed, virus production remained suppressed by > 70% for 3 to 4 days and following subsequent stimulation with PMA. In primary CD4+ T-cells obtained from PLWH, 10 µM hopeaphenol pre-treatment followed by wash-out significantly suppressed anti-CD3/CD28-induced supernatant viral RNA production by 50.7% ($p < 0.05$).
**Conclusion:** We show for the first time that hopeaphenol is a potent inhibitor of HIV transcription that acts on NF-κB-driven activation and CDK9 in target cells to inhibit viral production.

### 500 INTRINSIC RESISTANCE OF HIV-2 AND SIV TO THE MATURATION INHIBITOR GSK2838232

**Robert A. Smith**[1], Dana N. Raugi[1], Robbie Nixon[1], Jennifer Song[1], Moussa Seydi[2], Geoffrey S. Gottlieb[1]
*[1]University of Washington, Seattle, WA, USA, [2]Hospital Center National University de Fann, Dakar, Senegal*

**Background:** GSK2838232 (GSK232; GlaxoSmithKline) is a novel maturation inhibitor that blocks the proteolytic cleavage of the HIV-1 Gag-Pol precursor, rendering newly-formed virions non-infectious. GSK232 is active against a broad range of HIV-1 Gag variants in culture, including brevirimat-resistant mutants, and was recently evaluated in a Phase IIa clinical trial in HIV-1–infected individuals (NCT 03045861). To our knowledge, GSK232 has not been tested against HIV-2, and there are limited data regarding the susceptibility of HIV-2 to other compounds in the maturation inhibitor class.
**Methods:** We determined the activity of GSK232 against a panel of HIV-1, HIV-2, and SIV isolates using two culture-based methods: single-cycle assays, and 6-day spreading infections of an immortalized T cell line (CEMss). Single-cycle assays were initiated by transfecting GSK232-treated 293T-17 cells (and solvent-only controls) with full-length HIV or SIV-encoding plasmids. For the spreading (multi-cycle) assays, CEMss cells were treated with GSK232 and infected with cell-free virus stocks. To quantify replication-competent virus, supernatants from the 293T-17 and CEMss cultures were transferred to MAGIC-5A indicator cells. After ~44 h of growth, the MAGIC-5A monolayers were treated with lysis buffer, and HIV/SIV-induced β-galactosidase activity was quantified via the addition of a colorimetric substrate (CPRG). The resultant dose-response data were plotted in Prism v. 6.0h (GraphPad Software). All GSK232 preparations used in these experiments were purchased from Cayman Chemical (Ann Arbor, Michigan).
**Results:** GSK232 was highly active against HIV-1 isolates from group M subtypes A, B, C, D, F, and group O. $IC_{50}$ values for HIV-1 ranged from 1.5–3.7 nM in the single-cycle assay and 0.23–0.93 nM in spreading infection assays. In

contrast, GSK232 showed weak or no detectable activity ($IC_{50}$ >40 nM) against HIV-2 isolates from groups A, B, and CRF01_AB; similar results were observed for SIVmac239, SIVmac251, and SIVagm ($IC_{50}$ >40 nM).
**Conclusion:** GSK232 potently inhibited group M and group O isolates of HIV-1, but showed negligible activity against the HIV-2 and SIV strains tested in this study. The mechanism(s) responsible for the differential susceptibility of HIV-1 and HIV-2/SIV to GSK232 require further investigation. Our data suggest that GSK232 is not a suitable candidate for antiretroviral therapy of HIV-2 infection.



## 501 HIV-1 NONGROUP M PHENOTYPIC SUSCEPTIBILITY TO IBALIZUMAB (ANTI-CD4)

**Lucie Poisson-Arnaud**[1], Quentin Le Hingrat[2], Jean-Christophe Plantier[1], Elodie Alessandri-Gradt[1]
*[1]University of Rouen Normandy, Normandy, France, [2]Hôpital Bichat-Claude-Bernard, Paris, France*

**Background:** While HIV-1 group M is responsible for the large majority of HIV infections worldwide, 3 others groups named O, N and P (HIV-1 non-M) are more genetically divergent and concentrated in West-central Africa with sporadic cases in Europe, America and Canada. Previous works have demonstrated the limited number of therapeutic options due to the natural genetic polymorphisms associated with HIV-1 non-M. Thus, our work aimed to determine the in vitro susceptibility of these particular strains to Ibalizumab, a first-in-class long-acting CD4-directed post-attachment inhibitor.
**Methods:** Seven clinical isolates (5 HIV-1/O, 1 HIV-1/N and 1 HIV-1/P) were tested in parallel with the reference strain HIV-1/M BRU.HXB2. The phenotypic assay was performed by exposing Ibalizumab-preincubated PBMC to 100 TCID50 of viral supernatants for 2 hours. Cells were then washed and incubated in quadruplicate wells for 3 days in 5 increasing concentrations of Ibalizumab (1 – 10 000 ng/ml). Supernatants were collected and virus quantified by qRT-PCR for the calculation of inhibitory concentrations 50% ($IC_{50}$), maximum percent inhibition (MPI) and fold-change (FC).
**Results:** Five clinical isolates (4 HIV-1/O and 1 HIV-/N) had mean $IC_{50}$ (min; max) of 0.119 (6.10-11; 0.227) ng/ml and median MPI of 96.9%, comparable to those of the HIV-1/M reference ($IC_{50}$ and MPI of 0.186 ng/ml and 90.9% respectively). In contrast with these results, the RBF168 clinical isolate of HIV-1/P was naturally resistant ($IC_{50}$>10 000 ng/ml and MPI<25%), in two independent experiments. Finally, YBF17, a divergent clinical isolate of HIV-1/O subgroup H, had FC at 824 ($IC_{50}$ of 153 ng/ml) with intermediate MPI (75.9%) but within the susceptibility range defined in the literature for HIV-1/M (max at 600 ng/ml).
**Conclusion:** Our results demonstrate the susceptibility of HIV-1 non-M to Ibalizumab with 100% of susceptibility for HIV-1/O and N isolates but lack of activity against the only HIV-1/P tested. These results should now be confirmed in a larger panel and potential N-linked glycosylation sites (PNGS) should be assessed to determine their potential role in resistance of non-M HIV-1 to Ibalizumab. These data support the role of Ibalizumab as a potential treatment of group-O HIV patients.

## 503 SUSCEPTIBILITY TO 3BNC117 AND 10-1074 IN ART-SUPPRESSED CHRONICALLY INFECTED PERSONS

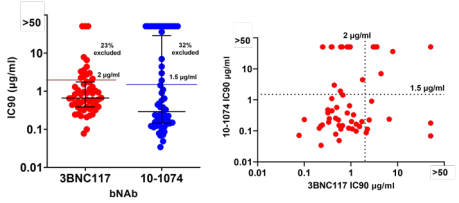
**Luis J. Montaner**[1], Kenneth Lynn[2], Livio Azzoni[1], Emmanouil Papasavvas[1], Matthew Fair[1], Giorgio Cocchella[2], Amanda Sciorillo[1], Charles Kang[3], Jacqueline D. Reeves[4], Linden Lalley-Chareczko[5], Jay R. Kostman[5], William R. Short[2], Karam Mounzer[5], Christos Petropoulos[4], Pablo Tebas[2]
*[1]Wistar Institute, Philadelphia, PA, USA, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]Labcorp-Monogram Biosciences, California, PA, USA, [4]Labcorp-Monogram Biosciences, San Francisco, CA, USA, [5]Philadelphia FIGHT, Philadelphia, PA, USA*

**Background:** Reduced susceptibility may limit the utility of broadly neutralizing anti-HIV monoclonal antibodies (bnAbs) in the prevention and treatment of HIV. At the present time, the PhenoSense mAb Assay is the only CLIA/CAP compliant screening test available to assess bnAb susceptibility in ARV suppressed individuals.
**Methods:** We used the PhenoSense mAb Assay, a phenotypic assay to assess the susceptibility of luciferase-reporter pseudovirions bearing populations of PBMC-derived HIV-1 envelope proteins to evaluate susceptibility to 3BNC117 and 10-1074 bnAbs. The results are expressed as the concentration of bnAb required to inhibit virus infectivity by 50%, 80%, 90% and 95% ($IC_{50}$, $IC_{80}$, $IC_{90}$ and $IC_{95}$, respectively), as well as the maximum percent inhibition (MPI). JRFL is used as an internal control. We evaluated mAb susceptibility for sensitivity to 3BNC117 and 101074 arbitrarily defined for the BEAT2 study (based in limited previous studies) as an $IC_{90}$ < 2.0 µg/mL for 3BNC117 and <1.5 µg/mL for 10-1074.
**Results:** We enrolled 61 ART suppressed (<20 copies/µL) participants with CD4+ T-cell counts ≥450 cells/µL and nadir >200 c/$mm_3$; 9 female, 1 transgender, 8 Caucasian (3/8 Hispanic), 53 African American. Nine of 61 (15%) did not amplify initially. Five of those were repeated and 2 amplified for a total of 54. Forty-one of 54 (76%) participants harbored virus exhibiting susceptibility to 3BNC117 and 37 of 54 (69%) exhibiting susceptibility to 10-1074. Thirty of 54 (56%, 95% CI 41-69)) were susceptible to both bnAbs and met study eligibility criteria. Although the $IC_{90}$ for 10-1074 was lower than 3BNC117, the

percentage of isolates with IC90 above the 10-1074 susceptibility cutoff was greater than the 3BNC117 cutoff (Figure). There was no correlation between bnAbs susceptibility (r=0.10 p=0.45 (Spearman)). Age, gender and race were no associated with susceptibility.

**Conclusion:** Approximately 50% of the chronically infected, virologically suppressed individuals harbored virus with reduced susceptibility to one or both of these mAbs. This is a potential limitation of combining only two bnAbs as PrEP or treatment, as a significant proportion of the circulating virus variants are likely to exhibit reduced susceptibility to at least one mAb. Further studies defining and validating the clinical correlates of bnAb susceptibility thresholds for therapeutic maintenance protocols and curative treatment strategies are urgently needed.

Figure: Left: Range of bnAb susceptibility of the isolates and proportion of subjects excluded based on reduced susceptibility to 3BNC117 and 10-1074. Right: Lack of correlation of 3BNC117 and 10-1074 bnAb susceptibility.




## 504 PERFORMANCE OF A PHENOTYPE AND 2 GENOTYPE ALGORITHMS FOR bNAb SENSITIVITY PREDICTION

New Investigator Scholar

**Marie H. Pahus**[1], Jesper D. Gunst[2], Victor Ramos[3], Martin Tolstrup[2], Jacqueline D. Reeves[4], Christos Petropoulos[4], Michel Nussenzweig[3], Marina Caskey[3], Ole Søgaard[2]

*[1]Aarhus University, Aarhus, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark, [3]The Rockefeller University, New York, NY, USA, [4]Labcorp-Monogram Biosciences Inc., South San Francisco, CA, USA*

**Background:** The use of broadly neutralizing antibodies (bNAbs) in HIV-1 cure-related clinical trials has greatly increased in recent years. Even though bNAbs are broadly neutralizing, not all HIV-1 variants are sensitive to a given bNAb due to tremendous viral diversity and development of escape mutations. Screening of participants for bNAb sensitivity before or after inclusion in a clinical trial is therefore crucial to obtain valid antibody efficacy data. Different assays are currently being used to screen bNAb sensitivity. Here we compare three different methods for bNAb sensitivity prediction of the two bNAbs: 10-1074 and 3BNC117.

**Methods:** The three methods tested in this study were the phenotypic "PhenoSense® HIV Monoclonal Antibody Assay" developed by Monogram Biosciences, and two genotypic prediction algorithms; the "HIV screening analysis" developed at Rockefeller University and the "bNAb-ReP" developed by VRC/NIH. The PhenoSense assay is a pseudovirus neutralization assay. The prediction pipelines were fed with intact HIV-1 envelope sequences from single genome amplification of HIV-1 envelope performed on pre-ART plasma RNA. The threshold for sensitivity in the PhenoSense assay was set to $IC_{90}$<1.5 µg/ml for 10-1074 and $IC_{90}$<2.0 µg/ml for 3BNC117. When using the genotypic prediction algorithms, a study participant was defined as harboring bNAb sensitive viruses if ≥90% of all envelope sequences were sensitive. Fifty-nine clinical samples from ART-naïve participants in the eCLEAR trial (NCT03041012) were evaluated.

**Results:** Concordant classification across all three methods were obtained for 79% and 52% of the participants for 10-1074 and 3BNC117, respectively. Comparing the HIV screening analysis and bNAb-ReP prediction algorithms to the PhenoSense assay, agreement for 10-1074 sensitivity was 87% and 83%, respectively, while agreement for 3BNC117 sensitivity was 60% and 75%, respectively. For 3BNC117, the HIV screening analysis was more likely to classify the envelope sequences as sensitive whereas, no pattern was observed for the bNAb-ReP pipeline.

**Conclusion:** We observed good agreement in bNAb sensitivity between the PhenoSense assay and both genotypic prediction algorithms for the V3-loop binding bNAb 10-1074. The agreement between phenotypic and genotypic sensitivity was lower for the CD4-binding site bNAb 3BNC117, which may pose greater challenges when screening participants for clinical studies and comparing results across different trials.

## 505 MUTATIONAL LANDSCAPE OF 10-1074 AND 3BNC117 SENSITIVITY IN A UK POPULATION WITH PHI

New Investigator Scholar

**Penny Zacharopoulou[1],** Lilian Nogueira[2], Thiago Oliveira[2], Helen Brown[1], Nicola Robinson[1], Sabine Kinloch-de Loes[3], Amanda Clarke[4], John Thornhill[5], Marina Caskey[2], Michel Nussenzweig[2], Julie Fox[6], Sarah Fidler[7], M. A. Ansari[1], John Frater[1]

*[1]University of Oxford, Oxford, UK, [2]The Rockefeller University, New York, NY, USA, [3]Royal Free Hospital, London, UK, [4]Brighton and Sussex University Hospitals NHS Trust, Brighton, UK, [5]Barts Health NHS Trust, London, UK, [6]Guy's and St Thomas' NHS Foundation Trust, London, UK, [7]Imperial College Healthcare NHS Trust, London, UK*

**Background:** 10-1074 and 3BNC117 are broadly neutralising antibodies (bNAbs), which target the V3 glycan and the CD4bs respectively, and together can maintain viral suppression after antiretroviral treatment (ART) interruption. Due to its high diversity rate and the dense array of glycans that shield the underlying bNAb epitopes, HIV can escape neutralisation. Although there is no established bNAb sensitivity screening method, several algorithms have identified certain genetic signatures that may predict potential bNAb sensitivity. Here, we aim to assess the utility of bNAb sensitivity screening for clinical trials and to present the distribution of 10-1074 and 3BNC117 sensitivity landscape in a UK cohort.

**Methods:** Samples from 173 participants diagnosed and treated during primary HIV infection (PHI), within an estimated 6 months of seroconversion were processed. All participants had been on ART for >1 year and had undetectable viral load at the time of sampling. An average of 20 proviral env sequences per sample was amplified using single genome amplification from 148 participants. Following sequencing, we inspected the amino acid residues that have been reported to confer resistance to 10-1074 (N332 glycosylation motif and 324GDIR327) and 3BNC117 (positions D279, N280 and 456RDGG459) epitopes.

**Results:** A total of 3138 proviral env sequences, mainly B clade (70.9%), were sequenced and analysed (Table). Mutations associated with resistance to either or both bNAbs were detected in 47.9% of participants and notably, 36.6% of these contained a mixture of both resistant and sensitive sequences. 66.1% of participants with resistant sequences had 10-1074 associated mutations. Mutations affecting the N332 glycosylation motif Asn-X-Ser/Thr were the most common 10-1074 resistance-associated mutations (85%). The most frequently mutated 3BNC117 sites were 456 and 459 (47.8% and 34.7%, respectively). There was however considerable variation between participants, including between those with mixed and full resistance. Phylogenetic analysis suggested evidence for both transmitted resistance and in-host evolution.

**Conclusion:** Our findings show that around half the cohort treated during PHI has potential pre-existing resistance to 10-1074 and 3BNC117 based on current algorithms. Although it is unclear how well these algorithms predict clinical response to bNAbs in real world settings, the suggestion from these data is that screening may be key to guide effective treatment.

| Env amplification status (of all participants in the cohort: n (%)) | | | |
|---|---|---|---|
| Amplified Env | | 148 (85.5%) | |
| Non-amplified Env | | 25 (14.4%) | |
| Clade (% of all participants with amplified env) | | | |
| B | | 105 (70.9%) | |
| Other (C, A1, F1, CRF01_AE, CRF02_AG) | | 43 (29%) | |
| Distribution of resistant sequences per participant | Any Sequence Resistant (% of all participants) | All sequences resistant (% of all resistant samples) | Mix of WT and resistant sequences (% of all resistant samples) |
| 10-1074 | 47 (66.1%) | 36 (50.7%) | 11 (15.5%) |
| 3BNC117 | 18 (25.4%) | 7 (9.9%) | 11 (15.5%) |
| Both | 6 (8.5%) | 2 (2.81%) | 4 (5.59%) |

## 506 EFFECT OF L74I POLYMORPHISM ON FITNESS OF HIV-1 SUBTYPE A6 RESISTANT TO CABOTEGRAVIR

**Zixin Hu[1],** Trevor Cordwell[1], Jerry Jeffrey[2], Daniel Kuritzkes[1]

*[1]Brigham and Women's Hospital, Boston, MA, USA, [2]ViiV Healthcare, Inc., Research Triangle Park, NC, USA*

**Background:** In Phase III clinical trials of long-acting (LA) Cabotegravir (CAB) and rilpivirine (RPV), subtype A6 virus, characterized by the L74I IN polymorphism, was associated with an increased risk of virologic failure. We investigated the effect of L74I on the viral replication capacity of recombinant viruses carrying this in combination with various InSTI resistance mutations.

**Methods:** Plasmids carrying HIV-1 NL4- deleted in pol were co-transfected into 293T cells together with IN from HIV-1 A6 carrying 74L or I in combination with various InSTI resistance mutations including G118R, G140R, Q148H, Q148K, Q148R, N155H and R263K, and the double mutation G140R/Q148R to generate

replication-competent recombinant viruses. Resulting virus stocks were titered on TZM-bl cells and replication capacity (RC) determined in the absence of and presence of CAB were performed in TZM-bl and MT-2 cells. Drug susceptibility to CAB was determined using a standard drug susceptibility testing protocol.
**Results:** Susceptibility to CAB of recombinant HIV-1 expressing the subtype A6 IN was similar whether L or I was present at position 74 ($IC_{50}$=1.36 nM and 1.10 nM, respectively). Recombinant viruses with 74L or 74I showed similar replication capacity on TZM-bl and MT-2 cells in the absence and presence of CAB (2 nM). In the absence of CAB, viruses carrying 74I outcompeted 74L viruses in growth competition assays, demonstrating greater fitness of L74I in an A6 IN context. Recombinants carrying the L74I polymorphism had significantly higher replication capacity in TZM-bl and MT-2 cells when present together with the G118R, G140R, Q148R and R263K InSTI resistance mutations; no significant difference in replication was observed for the Q148H or K mutants. Surprisingly, the opposite effect was observed with respect to N155H mutant, in which case the 74L variant showed greater replication capacity than 74I. Double mutants carrying G140R in combination with Q148R replicated too poorly in the context of either 74L or I to allow formal assessment of replication capacity.
**Conclusion:** Presence of the L74I polymorphism conferred greater replication capacity to recombinant viruses expressing HIV-1 A6 IN when present together with InSTI resistance mutations at positions 118, 140, 148 and 263. This finding may explain, in part, the association of HIV-1 subtype A6 and virologic failure observed in clinical trials of CAB-LA in combination with RPV-LA.

## 507 HOW MUTATIONS IN THE HIV-1 3′-POLYPURINE TRACT CONFER DOLUTEGRAVIR RESISTANCE

New Investigator Scholar

**Jose Dekker[1],** Bep Klaver[1], Ben Berkhout[1], Atze Das[1]
*[1]Amsterdam University Medical Center, Amsterdam, Netherlands*

**Background:** The integrase strand-transfer inhibitor (InSTI) dolutegravir (DTG) is widely applied in combination antiretroviral therapy for HIV-infected individuals. Resistance to DTG is usually associated with mutations in the integrase gene, but a previous in vitro HIV selection study identified a mutation in the 3'-polypurine tract (3'PPT) that reduced DTG sensitivity (Malet mBio 2017), and mutation of this viral sequence was also observed in a patient with virologic failure on DTG monotherapy (Wijting JID 2018) We predicted that such PPT mutations may affect the reverse transcription process (Das mBio 2018), in particular the start site of second-strand DNA synthesis and thereby the 5' end of the viral DNA that is the template for integration. We here set out to identify other PPT mutations that cause DTG resistance and to determine the molecular mechanism of PPT-mediated InSTI resistance.
**Methods:** We designed a library of HIV LAI genomes with a randomized PPT and selected virus variants that replicate in the presence of DTG in T cell lines. DTG resistance was demonstrated in single-cycle infection and virus replication experiments. Integrated and non-integrated viral DNA products were analyzed to investigate the effect of PPT-mutations on reverse transcription and integration.
**Results:** Culturing of this pool of PPT-variants on C8166 T cells in the presence of DTG resulted in the selection of viruses with different mutations in the 3'PPT. Single-cycle infection and multi-cycle replication experiments revealed that the selected 3'PPT mutations reduce viral fitness, yet improve virus replication with DTG. Intriguingly, replication of the 3'PPT-mutated viruses is activated by the HTLV-1 Tax protein that was recently shown to stimulate episomal (2-LTR circle) replication of an integrase-deficient HIV variant (Irwan mBio 2020)(Dekker AAC 2021). Analysis of the integrated and non-integrated viral DNA products formed upon infection indicates that the 3'PPT-mutations do not restore integration, but rather stimulate the production of such non-integrated HIV DNA products.
**Conclusion:** Our data indicate that several 3'PPT mutations cause DTG resistance. The mutations stimulate production of a non-integrating (episomal) DNA intermediate, which may allow a low level of integration-independent HIV replication. Further analysis of the mechanism of PPT-mediated DTG-resistance and the impact on viral fitness is important for a complete understanding of this potent and very popular drug class.

## 508 ABSENCE OF CROSS-RESISTANCE TO LENACAPAVIR IN HIV ENTRY INHIBITOR-RESISTANT ISOLATES

**Nicolas Margot[1],** Vidula Naik[1], Laurie VanderVeen[1], Martin Rhee[1], Christian Callebaut[1]
*[1]Gilead Sciences, Inc, Foster City, CA, USA*

**Background:** Lenacapavir (LEN) is a potent, first in class, multistage inhibitor of HIV-1 capsid function in clinical development. In people with HIV (PWH), LEN (50 mg to 750 mg) showed a rapid and strong antiviral effect, with up to 2.3 mean $log_{10}$ decrease in HIV-1 RNA at day 10. In people with multi-drug-resistant (MDR) HIV, subcutaneous (SC) LEN administered every 6 months in combination with other antiretroviral agents led to high rates of virologic suppression. LEN shows no cross resistance to HIV-1 isolates with resistance to the 4 main classes of ARVs or to maturation inhibitors. Here we have characterized the activity of LEN in HIV-1 isolates with phenotypic resistance to entry inhibitors (EIs).
**Methods:** HIV-1 isolates (n = 72) from PWH with MDR were tested for their phenotypic susceptibility to EIs maraviroc (MVC), fostemsavir (FTR), ibalizumab (IBA), and enfuvirtide (ENF, T20) using the PhenoSense Entry assay (Monogram Biosciences). Phenotypic resistance cutoffs for MVC and T20 were based on Monogram's assessment; resistance cutoffs for FTR and IBA were based on published data. The isolates were also tested in the Gag-Pro assay (Monogram) to determine their susceptibility to LEN and assess the potential impact of envelope-driven resistance to EIs on the susceptibility of the gag sequence from these isolates to LEN.
**Results:** Susceptibility data for FTR, IBA, T20, and MVC were obtained for 54, 58, 58, and 61 of the 72 isolates tested, respectively. Resistance to MVC was most prevalent (67.2%), followed by resistance to FTR and IBA (31.5% and 29.3%, respectively); Resistance to T20 was the least frequently observed (8.6%). Susceptibility data for LEN were obtained for 62 of the 72 isolates, with a mean overall susceptibility to LEN unchanged from wild-type (mean fold change [SD] = 1.0 [0.31], ranging from 0.3 to 1.7). Wild-type susceptibility to LEN was noted for all the isolates regardless of their level of resistance to EIs.
**Conclusion:** The gag sequence from EI-resistant isolates did not impact LEN susceptibility, indicating no association between EI resistance and LEN antiviral activity. These data, along with prior data showing no impact of resistance to the 4 main ARV classes (InSTI, NNRTI, NRTI, PI) and maturation inhibitors on LEN susceptibility, indicate that LEN does not show cross resistance to any of the classes of ARVs in clinical use. These findings support the use of LEN in combination with an optimized background regimen in PWH regardless of treatment history.

## 509 HIV DRUG RESISTANCE IN WOMEN RANDOMIZED TO DTG VS EFV OR TDF VS TAF IN PREGNANCY

**Ceejay L. Boyce[1]**, Sean Brummel[2], Lauren Ziemba[2], Katie McCarthy[3], Kevin Knowles[4], Sheila Styrchak[5], Renee Browning[6], Nahida Chakhtoura[7], Sikhulile Moyo[8], Tichaona Vhembo[9], Violet Korutaro[10], José H. Pilotto[11], Lameck Chinula[12], Shahin Lockman[13], Lisa M. Frenkel[5]
*[1]University of Washington, Seattle, WA, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]FHI 360, Durham, NC, USA, [4]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [5]Seattle Children's Research Institute, Seattle, WA, USA, [6]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [7]National Institute of Child Health and Human Development, Bethesda, MD, USA, [8]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [9]University of Zimbabwe, Harare, Zimbabwe, [10]Baylor College of Medicine Children's Foundation, Kampala, Uganda, [11]Hospital Geral de Nova Iguaçu, Rio de Janeiro, Brazil, [12]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [13]Brigham and Women's Hospital, Boston, MA, USA*

**Background:** Virologic failure (VF) and HIV drug resistance (HIVDR) in pregnant and postpartum women with dolutegravir (DTG)-containing antiretroviral treatment (ART) are not well described. We compared VF and HIVDR by study arm in IMPAACT 2010, a randomized trial of 3 ART regimens started in pregnancy (DTG+emtricitabine (FTC)/tenofovir alafenamide (TAF); DTG+FTC/tenofovir disoproxil fumarate (TDF); or efavirenz (EFV)/FTC/TDF.
**Methods:** IMPAACT 2010 enrolled 643 women with HIV who were ART-naive (with exception of prior PMTCT, PrEP, or ART for ≤14 days during screening) between 14-28 weeks gestation in 9 countries (88% African), and followed participants for 50 weeks postpartum. Maternal HIV RNA was measured at study entry, every 4 weeks antepartum, at delivery, and at 14, 28, 36, and 50 weeks postpartum. VF was defined as 2 consecutive HIV RNA tests ≥200 copies/mL at or after 24 weeks on study. In women with VF, plasma samples from screening and confirmed VF visits underwent consensus sequencing of HIV pol to examine regions encoding protease, reverse transcriptase, and integrase. Pairwise comparisons evaluated rates of VF (post-hoc) and HIVDR (Stanford algorithm) detected at VF between arms using the Wald test with 95% confidence intervals. HIVDR mutations pre-randomization and new mutations at VF are described.

**Results:** Both DTG arms had significantly lower rates of VF and HIVDR at VF compared to the EFV arm (Table). Of 42 women with VF, 35 (83%) were successfully genotyped and 19/35 (54%) had HIVDR at VF. HIVDR mutations were detected at study entry in 15/19 (79%) women with resistance at VF (10/13 randomized to EFV and 5/6 to DTG). At VF, new HIVDR mutations were detected in 9/19 women; 7/13 (54%) women on EFV, all 7 with EFV-associated mutations (K103N, V106M, or P225H) and 2/7 with NRTI-associated mutations (K65R, Y115F, and/or M184V); and 2/6 (33%) on DTG, with detection of the major DTG-associated mutation N155H and accessory mutations (L74I, S147G, and S230R) in one, and an NNRTI-associated mutation (K103N) in the other.

**Conclusion:** HIVDR mutations were present at study entry in the majority of women with subsequent VF after ART initiation in pregnancy, and may have contributed to VF. Women in the EFV arm were more likely to experience VF and to select new HIVDR mutations at VF compared to the DTG arms. While VF was uncommon with DTG, it is notable that mutations to DTG were seen in one woman during a relatively short treatment period.

**Table: Comparison of Virologic Failure and HIV Drug Resistance Rates at Failure Between Treatment Groups**

| | DTG+FTC/TAF n/N (%) | DTG+FTC/TDF n/N (%) | EFV/FTC/TDF n/N (%) | Comparison | Difference in Proportions (95% CI) | P-Value |
|---|---|---|---|---|---|---|
| Virologic Failure | 9/217 (4.1%) | 11/215 (5.1%) | | DTG+FTC/TAF vs DTG+FTC/TDF | -1.0% (-4.9%, 3.0%) | 0.63 |
| | | 11/215 (5.1%) | 22/211 (10.4%) | DTG+FTC/TDF vs EFV/FTC/TDF | -5.3% (-10.4%, -0.2%) | 0.040 |
| | 9/217 (4.1%) | | 22/211 (10.4%) | DTG+FTC/TAF vs EFV/FTC/TDF | -6.3% (-11.2%, -1.4%) | 0.012 |
| Any HIV Drug Resistance | 2/217 (0.9%) | 4/215 (1.9%) | | DTG+FTC/TAF vs DTG+FTC/TDF | -0.9% (-3.1%, 1.3%) | 0.40 |
| | | 4/215 (1.9%) | 13/211 (6.2%) | DTG+FTC/TDF vs EFV/FTC/TDF | -4.3% (-8.0%, -0.6%) | 0.023 |
| | 2/217 (0.9%) | | 13/211 (6.2%) | DTG+FTC/TAF vs EFV/FTC/TDF | -5.2% (-8.7%, -1.8%) | 0.0032 |

## 510 A RANDOMIZED TRIAL OF DTG PLUS DRV/c AS A SWITCH STRATEGY IN SUBJECTS WITH MDR HIV-1

**José Ramón Santos**[1], Pere Domingo[2], Joaquín Portilla[3], Félix Gutiérrez[4], Arkaitz Imaz[5], Helem H. Vilchez[6], Adrià Curran[7], Nieves Valcarce[8], Antoni Payeras[9], Enrique Bernal[10], Marta Montero[11], Miguel Ysuski[12], Roger Paredes[13]
*[1]Hospital Germans Trias i Pujol, Barcelona, Spain, [2]Hospital de Sant Pau, Barcelona, Spain, [3]Hospital General Universitario de Alicante, Alicante, Spain, [4]Hospital General Universitario de Elche, Elche, Spain, [5]Hospital Universitario de Bellvitge, Barcelona, Spain, [6]Hospital Universitario de Son Espases, Palma de Mallorca, Spain, 7Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [8]Hospital Arquitecto Marcide, Ferrol, Spain, [9]Hospital Son Llàtzer, Palma de Mallorca, Spain, [10]Hospital Universitario Reina Sofia, Murcia, Spain, [11]Hospital Universitario y Politecnico La Fe, Valencia, Spain, [12]Hospital General Nuestra Señora del Prado, Talavera de la Reina, Spain, [13]IrsiCaixa Institute for AIDS Research, Badalona, Spain*

**Background:** Dual therapy with DTG+DRV/c may be a suitable ART simplification strategy for treatment-experienced subjects with drug resistance mutations (DRM) because both drugs have high genetic barrier to resistance and can be given once daily. This clinical trial evaluated the efficacy and safety of switching to DTG+DRV/c as a 2-pill once-daily simplification strategy in well-suppressed and highly ART-experienced patients harboring archived DRM against at least two antiretroviral classes.

**Methods:** Adults on ART containing at least 3 antiretroviral drugs, confirmed HIV-1 RNA <50 c/ml for ≥6 months preceding the randomization, history of DRM against at least 2 antiretroviral classes, with no integrase-associated mutations or previous virological failure (VF) to InSTI-based regimens and no evidence of significante resistance to DRV (<15 points from Stanford dB score) were randomized 1:1 to switch to open-label DTG+DRV/c or to continue baseline regimen. The primary endpoint was the percentage of subjects with HIV-1 RNA <50 c/mL at week 48 by TLOVR. Sensitivity analysis at week 48 was done using the FDA snapshot algorithm. VF was defined as confirmed HIV-1 RNA ≥50 c/mL or a single determination of HIV-1 RNA >1000 c/mL.

**Results:** 45 and 44 subjects were assigned to the dual therapy and control arms respectively. Participants had a mean (SD) of 13.2 (4.1) previous ART regimens and a median (IQR) time of 57 (24.5; 112) months with sustained viral suppression. In the TLOVR analysis, there was no difference in the proportion of subjects maintaining HIV-1 RNA <50 c/mL at week 48 (95.6% vs 90.9%, log rank p=0.392). There was no VF in the DTG+DRV/c group, whilst there were 2 (4.5%) VF in the control group (p=0.147, snapshot analysis). No significant differences were found between groups in renal function and lipid profile from baseline. Adverse events (arthralgias, diarrhea, rash) leading to treatment discontinuation were observed in 3 subjects from the DTG+DRV/c group and none in the controls. ART adherence remained above 98% in both study arms.

**Conclusion:** Dual therapy with DTG+DRV/c maintains viral suppression in highly treatment experienced subjects with multiclass drug resistance, as long as they retain DRV- and InSTI-susceptible HIV-1.

## 511 LOW-LEVEL RESISTANCE MUTATIONS CORRELATE WITH HIV THERAPY FAILURE IN PREGNANT WOMEN

**Rachel M. Burdorf**[1], Shuntai Zhou[1], Claire Amon[1], Collin Hill[1], Lily Adams[1], Gerald Tegha[2], Maganizo Chagomerana[2], Allan Jumbe[2], Madalitso Maliwichi[2], Shaphil Wallie[2], Sarah B. Joseph[1], Ronald Swanstrom[1], Mina C. Hosseinipour[2]
*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]University of North Carolina at Chapel Hill School of Medicine Project-Malawi, Lilongwe, Malawi*

**Background:** HIV drug resistance mutations (DRMs) can be acquired by transmission, during untreated infection, or during antiretroviral therapy (ART) if ART adherence is poor. High frequency DRMs are known risk factors for treatment failure (TF), but the association between low frequency DRMs and TF has not been examined. We explore this association using sequencing methods that can distinguish low frequency DRMs from sequencing errors.

**Methods:** We enrolled HIV+ pregnant women in Malawi who were either ART experienced but off treatment at entry or ART naïve. At entry, all started a TDF/3TC/EFV regimen. TF was defined as either suppression followed by rebound or failure to suppress (>40 copies/mL) by 6 months. We used MiSeq with Primer ID to sequence codons 34-236 of reverse transcriptase (RT) to identify DRMs in entry plasma samples. This approach links each RNA genome with a unique tag to correct sequencing errors and define sampling depth. We used Kaplan-Meier methods to explore whether TF was associated with either previous ART treatment or the presence of DRMs (K65R, K103N and M184V). Hazard ratios (HRs) for DRMs and viral load at entry were estimated using a Cox proportional-hazards model adjusting for previous ART exposure. Separate analyses were performed at DRM detection sensitivities of 10% and 3% based on sampling depth.

**Results:** Sequence data were analyzed from ART naïve (N=137) and ART experienced participants (N=79). Over time, experienced participants were significantly more likely to have TF (21/79, 26.6%) than naïve participants (20/137, 14.6%; p< 0.01). Experienced participants still had a higher risk of TF even when incidence of TF was stratified by previous ART (p< 0.01; Fig. 1A). The presence of DRMs was significantly associated with TF risk at both 10% (p< 0.01; Fig. 1B) and 3% sensitivity (p=.002). K103N was also associated with TF at both sensitivity levels (10% shown in Fig. 1C) and remained an independent risk factor after stratification for previous ART with an HR of 2.6 [1.0-6.7] at 10% (Fig. 1D) and 4.6 [1.5-14.3] at 3%. The presence of M184V significantly increased TF risk (p< 0.01) at 3% sensitivity, but not after stratification (Fig 1D).

**Conclusion:** Both previous ART experience and the presence of DRMs were associated with increased TF rates. K103N increased risk of TF regardless of ART experience. Additionally, high overall failure rates among ART experienced women who were off treatment at entry indicate adherence is an important factor in TF.

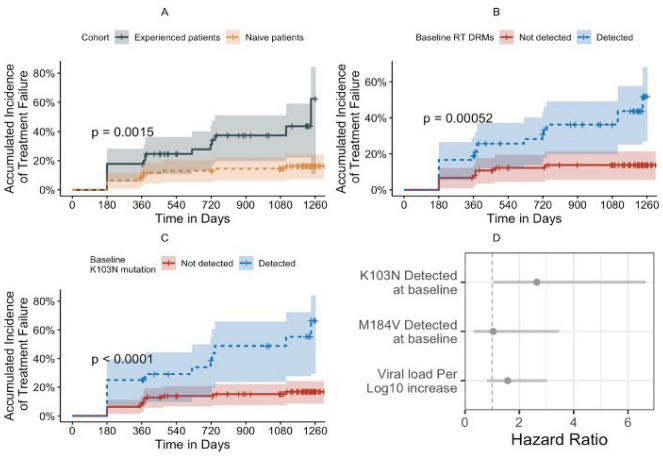



Fig. 1: **DRMs and previous ART experience impact treatment failure.** All data drawn from 10% DRM detection sensitivity level. (a) ART-Experienced vs. ART-naïve patients differ in treatment failure rate. (b) Presence of reverse transcriptase-relevant DRMs at entry significantly increases likelihood of treatment failure. (c) Presence of K103N mutation at entry significantly increases likelihood of treatment failure. (d) Presence of K103N mutation at entry conveys a hazard ratio of 2.64 (1.05-6.65, p = 0.04). Presence of M184V mutation at entry conveys a hazard ratio of 1.0 (0.31-3.47, p = 0.95). Every log10 increase of baseline viral load at entry conveys a hazard ratio of 1.57 (0.81-3.01, p = 0.18).

## 512 CHANGES IN THE HIV-1 3'-PPT IN PATIENTS FAILING DOLUTEGRAVIR IN BRAZIL

**Jeroen J. van Kampen**[1], Rob Gruters[1], Saye Khoo[2], Daniel Kuritzkes[3], Ricardo S. Diaz[4], James Hunter[4], Thibault Mesplede[1], David van de Vijver[1], Jolanda Voermans[1], Ben Berkhout[5], Atze Das[5], Mauro Schechter[4]
*[1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]University of Liverpool, Liverpool, UK, [3]Brigham and Women's Hospital, Boston, MA, USA, [4]University of Sao Paulo, Sao Paulo, Brazil, [5]Amsterdam University Medical Center, Amsterdam, Netherlands*

**Background:** The 3'-polypurine tract (3'-PPT) is a conserved 15 nucleotide long region of the HIV genome. In vitro studies have shown that mutations in the 3'-PPT can cause high level resistance to dolutegravir (DTG) and other integrase strand-transfer inhibitors (InSTI). Whether mutations in the 3'-PPT also lead to InSTI resistance in HIV-1 infected patients is still under debate. Here we determined the 3'-PPT sequences of HIV-1 in patients failing DTG-containing combined-antiretroviral therapy (cART) in Brazil.

**Methods:** The 3'-PPT sequences of HIV-1 from 67 patients failing DTG-containing cART were obtained by Sanger sequencing of total nucleic acid isolated from EDTA whole blood. Phylogenetic analysis was used to rule out cross-contamination in the 3'-PPT sequencing procedure. For all 3'-PPT sequences that deviated from the consensus 3'-PPT sequence, we calculated the frequency of the observed mutations in 3123 HIV-1 sequences from the Los Alamos database (2018, all subtypes). The binomial distribution was used to calculate the probability of obtaining a particular number of mutations given the frequency obtained from Los Alamos.

**Results:** From 45 patients, the HIV-1 3'-PPT sequences were obtained. Results from the remaining 22 patients are pending. From the 45 patients, 39 had the consensus 3'-PPT sequence and 6 patients had one or two nucleotide substitutions in this sequence (see Table). In 3 patients we observed an A → G mutation at the 3rd position of the 3'-PPT, which was also found in 7% of the 3123 sequences (p=0.23) from the Los Alamos database. The A → G mutation at the 4th position, the A → C mutation at the 8th position, and the A → C mutation at the 9th position of the 3'-PPT were found in 0.2% (p=0.08), 1.1% (p=0.07), and 0.2% (p=0.08) of the 3123 sequences from the Los Alamos database, respectively.

**Conclusion:** In 6 of the 45 patients failing DTG, we detected mutations in the 3'-PPT. In 3 of these patients, a transition at the 3rd position of the 3'-PPT was detected, which is a polymorphic mutation based on comparison with HIV-1 sequences from the Los Alamos database. In the remaining 3 patients, mutations were detected at the 8th or 9th position of the 3'-PPT (borderline significant due to low numbers), which are relatively conserved suggesting selection of these mutations by selective pressure of DTG. The phenotypic effect of the 3'-PPT mutations detected here on InSTI susceptibility and HIV-1 replication capacity are still unknown and will be investigated further.

| | |
|---|---|
| consensus 3'-PPT | A AAA GAA AAG GGG GG |
| Patient_12 | A AGR GAA AAG GGG GG |
| Patient_19 | A AGA GAA AAG GGG GG |
| Patient_29 | A AGA GAA AAG GGG GG |
| Patient_31 | A AAA GAA CAG GGG GG |
| Patient_34 | A AAA GAA ACG GGG GG |
| Patient_45 | A AAA GAA MAG GGG GG |

## 513 TEMPORAL VARIABILITY OF MULTI-CLASS RESISTANT HIV-1 IN PROVIRAL DNA

**Christian Hoffmann**[1], Eva Wolf[2], Patrick Braun[3], Markus Bickel[4], Albrecht Stoehr[5], Silke Heldwein[6], Heribert Knechten[3], Stefan Esser[7], Christoph Mayr[8], Christoph Wyen[9], Markus Mueller[10], Jan-Christian Wasmuth[11], Maximilian Münchhoff[12], Alexander Thielen[13], Martin Daeumer[13]
*[1]ICH Study Center, Hamburg, Germany, [2]MUC Research, Munich, Germany, [3]PZB, Aachen, Germany, [4]Infektiologikum, Frankfurt, Germany, [5]Institute of Immunology, Hamburg, Germany, [6]MVZ Goetheplatz, Munich, Germany, [7]University of Duisburg-Essen, Essen, Germany, [8]Zentrum für Infektiologie Berlin Prenzlauer Berg, Berlin, Germany, [9]Praxis Ebertsplatz, Cologne, Germany, [10]Praxis Tuebingen, Tuebingen, Germany, [11]University of Bonn, Bonn, Germany, [12]Ludwig Maximilian University, Munich, Germany, [13]Institute of Immunology and Genetics, Kaiserslautern, Germany*

**Background:** Little is known on the evolution of archived drug resistance-associated mutations (RAMs) in proviral DNA of patients with multi-class resistant HIV-1 and sustained viral suppression (VS).

**Methods:** In a multicentric study of patients with major 'historical' RAMs according to Stanford-HIVdb v8.6.1 in ≥3 ARV classes (of NRTIs, NNRTIs, PIs, InSTIs), tropism and mutational patterns in proviral DNA were evaluated in 2017 and 2020. Applying different detection cut-offs after APOBEC filtering, detection rates of cumulative RAMs from previous plasma resistance testings were assessed.

**Results:** The analysis included 96 patients (84 males, 12 females) with a median of 10 historical RAMs (IQR 8-11) and without any reported ART interruption or transient viremia at least three years prior to the first sample, among them 63 without any ART modification. Median time of sustained viral suppression (VS) was 9.0 years. Applying a cut-off of 1% and 15%, respectively, proviral DNA yielded an overall detection rate of 76% and 63% for 872 historical RAMs, as well as 164 (+19%) and 62 (+7%) previously undetected RAMs (see Table). We found a high intra-individual variability and divergence of the proviral genotype over time. In only 26/96 patients, at least 75% of historical RAMs were detected at both time points. The majority displayed mixed and temporally divergent patterns, including 22/96 patients in which more historical RAMs were detected in 2020, compared to 2017. Median individual detection rate was higher in patients with a low CD4 T-cell nadir (< vs ≥ 50/µl: 91% vs 83%), lower CD4 T-cell count in 2020 (< vs ≥ 750/µl: 89% vs 74%) and X4 tropism (90% vs 75%), but was not associated with level of proviral DNA, time of VS, time of virological failure, or current ARV regimen. In an ordinal logistic regression analysis, using a cut-off of 1%, only confirmed X4 tropism (OR 3.8, 95%CI 1.3-11.2, p=0.01) was significantly associated with a higher detection rate of historical RAMs.

**Conclusion:** Among patients with multi-class resistant HIV-1 and sustained viral suppression, proviral DNA genotypes yielded relative high detection rates for historical RAMs and an additional 19% of previously unknown RAMs. However, there was a considerable temporal variability, and in many subjects, mutational pattern changes appeared non-directional and unaffected by ARV regimen. Our results argue against treatment decisions and de-escalation strategies in this population, based on proviral genotyping alone.

| | NRTI-RAMs (n=430) | NNRTI-RAMs (n=142) | PI-RAMs (n=290) | INSTI-RAMs (n=10) |
|---|---|---|---|---|
| *Detection of historical RAMs, **cut-off 1%**, absolute numbers (Detection rates among drug class)* | | | | |
| Both time points, in 2017 and 2020 | 230 (53%) | 41 (29%) | 109 (38%) | 2 (20%) |
| 2017 only | 78 (18%) | 27 (19%) | 67 (23%) | 1 (10%) |
| 2020 only | 55 (13%) | 22 (15%) | 33 (11%) | 2 (20%) |
| Never detected | 67 (16%) | 52 (37%) | 81 (28%) | 5 (50%) |
| *Detection of historical RAMs, **cut-off 15%**, absolute numbers (Detection rates among drug class)* | | | | |
| Both time points, in 2017 and 2020 | 190 (44%) | 36 (25%) | 80 (28%) | 1 (10%) |
| 2017 only | 58 (13%) | 19 (13%) | 42 (14%) | 0 |
| 2020 only | 63 (15%) | 19 (13%) | 37 (13%) | 3 (30%) |
| Never detected | 119 (28%) | 68 (48%) | 131 (45%) | 6 (60%) |
| *Detection of previously unknown RAMs, cut-off 1%, absolute numbers (% among drug class)* | | | | |
| Both time points, in 2017 and 2020 | 16 (29%) | 3 (9%) | 6 (12%) | 2 (8%) |
| 2017 only | 17 (30%) | 15 (44%) | 22 (46%) | 9 (35%) |
| 2020 only | 23 (41%) | 16 (47%) | 20 (42%) | 15 (58%) |

## 514 COMPARATIVE ANALYSIS OF HIV-1 RNA AND ARCHIVED PROVIRAL HIV-1 DNA GENOTYPING

**Noah C. Gaitan**[1], Michelle L. D'Antoni[2], Rima K. Acosta[2], Susan J. Little[1], Antoine Chaillon[1]

*[1]University of California San Diego, La Jolla, CA, USA, [2]Gilead Sciences, Inc, Foster City, CA, USA*

**Background:** Bulk genotyping of blood plasma (BP) is routinely used to identify HIV drug resistance mutations (DRMs) to determine appropriate antiretroviral treatment (ART). Yet, the benefit of genotyping archived proviral DNA to detect preexisting DRMs is not well characterized. Here, we investigated whether deep sequencing of archived proviral HIV DNA in PBMC before ART initiation among recently infected adults can identify mutations not detected in BP. Notably, among ART-naïve, recently infected persons, DRM are most likely to be identified in populations of the transmitted/founder virus that have evolved under natural selection.

**Methods:** We performed deep sequencing of HIV DNA (Seq-IT, Germany) from pre-ART HIV DNA sampled from adults enrolled in the San Diego Primary Infection Research Consortium (PIRC). APOBEC hypermutation-filtered reads were analyzed to identify DRMs for NRTI, NNRTI, and InSTI mutations. We compared the prevalence of minority (2-20%) and majority (>20%) NNRTI/NRTI mutations found in archived proviral DNA in PBMC and HIV RNA from paired BP (bulk population sequencing).

**Results:** In total, we analyzed pre-ART HIV RNA and DNA samples from 190 individuals with recent HIV infection. Thirteen NNRTI and 9 NRTI mutations were found only in HIV DNA. The remaining 27 NNRTI/NRTI mutations appeared in both HIV DNA and BP (Fig.1A). Notably, while 2 major M184V mutations appeared in both PBMC and BP samples, 6 low-frequency M184I were found only in HIV DNA. All major DRMs (>20%), except for 2 K103N mutations, were found in both HIV DNA and BP. Eleven InSTI DRMs (>2%) were also detected in HIV DNA from PBMC (Fig.1B). Among participants with preexisting DRMs, early initiation of an empirical ART regimen did not lead to virologic failure during the follow-up period (25.39 ± 3.13 months).

**Conclusion:** In our study, early ART initiation in recently infected individuals was not associated with any virologic failure in participants with archived DRMs and may have limited the diversification of viral quasispecies and the emergence of resistant variants. In addition to effectively identifying DRMs through routine pre-ART genotyping, deep sequencing of HIV DNA also identified 22 low-frequency mutations and 2 major K103N mutations that were not detected in paired BP. These results illustrate that even in the absence of detectable NNRTI resistance by routine bulk sequencing, caution should be used if choosing an NNRTI for treatment.

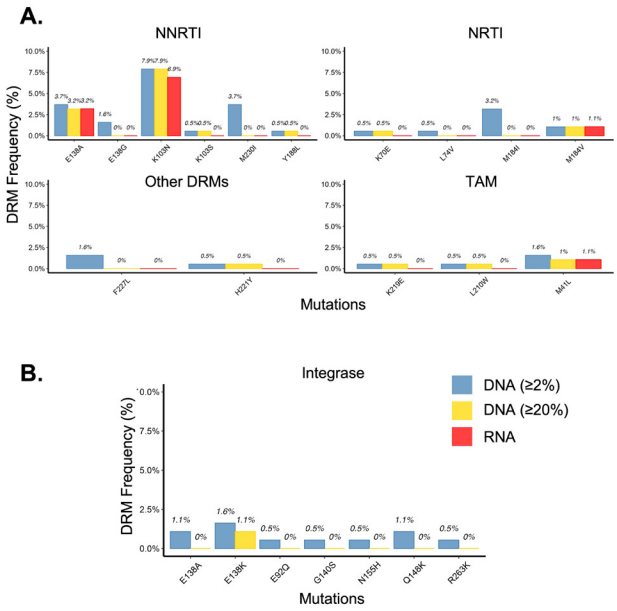



**Figure 1A. DRM frequency (%) of NNRTI/NRTI mutations in archived proviral DNA and blood plasma (BP).** All low frequency (blue: 2-20%) and major (yellow: >20%) mutations detected in proviral DNA from the 190 participants are included. Mutations present in BP are denoted in red. **B. DRM frequency (%) of INSTI mutations in archived proviral DNA.** All low frequency and major mutations detected in proviral DNA are included.

## 515 POINT-OF-CARE URINE TENOFOVIR TESTING TO DETECT HIV DRUG RESISTANCE

**Suzanne McCluskey[1],** Katya Govender[2], John Adamson[2], Monica Gandhi[3], Matthew A. Spinelli[3], Mahomed-Yunus Moosa[4], Henry Sunpath[4], Pravikrishnen Moodley[4], Melendhran Pillay[5], Selvan Pillay[6], Winnie R. Muyindike[7], Godfrey Masette[7], Bethany Hedt-Gauthier[8], Vincent Marconi[9], Mark Siedner[1]

*[1]Massachusetts General Hospital, Boston, MA, USA, [2]Africa Health Research Institute, Mtubatuba, South Africa, [3]University of California San Francisco, San Francisco, CA, USA, [4]University of KwaZulu-Natal, Durban, South Africa, [5]National Health Laboratory Service, Durban, South Africa, [6]Adrenergy Research Innovations, Durban, South Africa, [7]Mbarara University of Science and Technology, Mbarara, Uganda, [8]Harvard Medical School, Boston, MA, USA, [9]Emory University, Atlanta, GA, USA*

**Background:** Genotypic resistance testing (GRT) is not included in management guidelines for those with virologic failure on first-line antiretroviral therapy (ART) in sub-Saharan Africa due to high costs and low availability in the region. The objective of this study was to evaluate the utility of a point-of-care (POC) urine tenofovir (TFV) assay to detect HIV drug resistance (HIVDR) for patients failing first-line therapy.

**Methods:** We retrospectively tested specimens that were collected during the REVAMP clinical trial, which enrolled adults ≥18 years at public-sector clinics in Uganda and South Africa who experienced virologic failure on first-line therapy with non-nucleoside reverse transcriptase inhibitors. Blood and urine specimens were collected and stored at each visit. GRT using Sanger sequencing was performed in plasma specimens from the enrollment and nine-month visits when HIV-1 RNA viral load was >1,000 copies/ml. For this analysis, we tested urine specimens from participants in South Africa on TFV-containing first-line ART for which paired GRT results were available. We assessed recent ART adherence as the predictor of interest by measuring presence versus absence of TFV in urine using a POC lateral flow assay with a cut-off value of 1,500 ng/ml. We calculated test performance characteristics of the POC urine TFV assay to detect HIVDR, defined as intermediate or high-level resistance to the current ART regimen, determined by the Stanford algorithm. We also calculated positive and negative predictive values across a range of HIVDR prevalence estimates.

**Results:** We analyzed 135 urine specimens with paired plasma GRT results from 135 participants with a median age of 38 years (IQR 31-44); 44% were female. Median duration of ART at the time of first-line virologic failure was 4.4 years (IQR 3.5-6.8), and the most common ART regimen was emtricitabine, tenofovir, and efavirenz. Overall, prevalence of HIVDR was 88% (n=119/135). Of those with TFV detected on the POC assay, 96% (n=94/98) had HIVDR, versus only 68% (n=25/37) with HIVDR in those with no TFV detected (p value<0.001). Test

characteristics, including positive and negative predictive value for a range of HIVDR prevalence estimates, are shown in the Table.

**Conclusion:** In settings with a high prevalence of HIVDR, the POC urine TFV lateral flow assay could provide a novel, low-cost method to confirm HIVDR, guide who needs resistance testing, and inform the need to switch to second-line ART.

**Table. Point-of-Care Urine Tenofovir Test Characteristics to Detect HIV Drug Resistance**

| Test Characteristics | | HIVDR Prevalence Estimates | PPV | NPV |
|---|---|---|---|---|
| Sensitivity | 79% | 90% | 97% | 28% |
| Specificity | 75% | 75% | 90% | 54% |
| PPV | 96% | 50% | 76% | 78% |
| NPV | 32% | 25% | 51% | 91% |
| *Observed HIVDR Prevalence* | *88%* | 10% | 26% | 97% |

HIVDR=HIV drug resistance, PPV=positive predictive value, NPV=negative predictive value

## 516 TRANSMITTED DRUG RESISTANCE TO INTEGRASE-BASED FIRST-LINE TREATMENT IN EUROPE

**Adolfo De Salazar**[1], Laura Viñuela[1], Ana Fuentes[1], Elisa Teyssou[2], Charlotte Charpentier[3], Sidonie Lambert-Niclot[4], Lavinia Fabeni[5], Carlo F. Perno[6], Dimitrios Paraskevis[7], Perpetua Gomes[8], Maria M. Santoro[9], Francesca Ceccherini-Silberstein[9], Anne Genevieve Marcelin[2], Federico Garcia[1]

*[1]Hospital Universitario San Cecilio, Granada, Spain, [2]Hôpitaux Universitaires Pitié Salpêtrière, Paris, France, [3]Hôpital Bichat-Claude-Bernard, Paris, France, [4]Saint-Antoine Hospital, Paris, France, [5]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [6]Bambino Gesu Children's Hospital, Rome, Italy, [7]National and Kapodistrian University of Athens, Athens, Greece, [8]Instituto Universitário Egas Moniz, Lisboa, Portugal, [9]University of Rome Tor Vergata, Rome, Italy*

**Background:** Integrase strand-transfer inhibitors (InSTIs) based regimens are recommended regimens for first-line antiretroviral therapy. Our objective has been to study the prevalence of transmitted drug resistance to the InSTIs and the NRTI backbone in newly diagnosed patients that are naïve to antiretroviral therapy (ART).

**Methods:** MeditRes HIV is a consortium that includes ART naïve people living with HIV that have been newly diagnosed in France, Greece, Italy, Portugal and Spain during the years 2018-2021. Reverse transcriptase (RT), protease (Pro) and Integrase were sequenced following standard methodologies in use at the participating centres. To evaluate the prevalence of surveillance drug resistance mutations (SDRM) we used the Calibrated Population Resistance (CPR) tools (integrase and RT-Pro) available at Stanford HIV website. To evaluate clinically relevant transmitted resistance, we used the Stanford v.9.0 HIVDB Algorithm.

**Results:** Overall, we included 2657 patients with integrase and RT data available. At diagnosis, 78% were men, median age was 37 (IQR, 30-48) and median viral load was 108.006 copies/mL (IQR, 25.350-420968); 42.43% of the patients were infected by non-B subtypes. The prevalence of InSTI SDRMs was 0.23% (T66I, n=1; T66A, n=1; E138T, n=1, E138K n=1, E92Q n=1 and R263K n=1). The prevalence of NRTI SDRMs was 3.76% (M184V n=21, 0.81%; M184I n=5. 0.19%; K65R n= 1, 0.04%; any TAMS n=71, 2.72%). Clinically relevant resistance, defined as any resistance level for Stanford interpretation >= 3, was 2.42% for InSTIs (0.19% to Dolutegravir and Bictegravir; 2.38% to Raltegravir; 2.42% to Elvitegravir), and 1.76% to the components of the NRTI backbones (0.88% to TDF/TAF; 1.76% to Abacavir; 1.15% to Lamivudine/Emtricitabine).

**Conclusion:** Here we describe the most recent data on transmitted drug resistance to integrase based first line regimens in Mediterranean Europe. Given the low prevalence of clinically relevant resistance to second generation integrase inhibitors and to first line NRTIs, in the years 2018-2021 it is very unlikely that a newly diagnosed patient in MeditRes countries would present with baseline resistance to a first line regimen based on second generation integrase inhibitors.

## 517 STATEWIDE TRENDS OF TRANSMITTED HIV-1 DRUG RESISTANCE IN RHODE ISLAND OVER 2004-2020

**Vlad Novitsky**[1], Jon Steingrimsson[1], Fizza S. Gillani[1], Mark Howison[2], Su Aung[1], Cindy Y. Won[1], Amy Brotherton[1], Rajeev Shah[1], Thomas Bertrand[3], Anna Civitarese[3], Katharine Howe, Utpala Bandy[3], Nicole Alexander-Scott[3], Joseph Hogan[1], Rami Kantor[1]

*[1]Brown University, Providence, RI, USA, [2]Research Improving People's Life, Providence, RI, USA, [3]Rhode Island Department of Health, Providence, RI, USA*

**Background:** HIV-1 transmitted drug resistance (TDR) remains a roadblock toward ending the HIV epidemic due to its ability to compromise effectiveness of antiretrovirals for prevention and care. Country- and state-wide TDR data beyond selected surveillance and research efforts are absent, and available estimates are heterogenous.

**Methods:** We aggregated all available HIV-1 pol partial sequences from treatment-naïve persons receiving routine clinical care in the state of Rhode Island over 2004–2020, and evaluated statewide TDR extent, trends, impact on 1st-line regimens, and association with transmission networks, by using Stanford Database tools, Mann-Kendall statistic, and phylogenetic analysis.

**Results:** A total of 1,123 treatment-naïve persons, ~86% of all new-HIV diagnoses in Rhode Island in 2004-2020 had available sequences. Statewide TDR to any antiretroviral drug increased from 8% (2004) to 26% (2020; Mann-Kendall statistic 0.47, 95% confidence interval (CI) 0.16–0.68). TDR trends were mostly driven by NNRTI-associated mutations (steady increase from 5% in 2004 to 18% in 2020; Mann-Kendall statistic 0.48, 95% CI 0.16–0.69; K103N/S most prominent), less by NRTI-associated mutations (increase from 2% in 2004 to ~8% in 2020; Mann-Kendall statistic 0.074, 95% CI -0.21–0.32; K65R absent, M184V/I 0.5%); and even less by PI-associated mutations (from <2% in mid-2000's to 7% in 2008 and ~2-3% in 2019-2020; Mann-Kendall statistic 0.21, 95% CI -0.15–0.49). Dual- and triple-class TDR were low and major InSTI TDR was absent. Predicted intermediate-high resistance to 1st-line regimens was in 77% of people with TDR, with differential viral load suppression patterns after 1st-line initiation. Among all individuals, 34% were in molecular clusters; and 14% of all clusters included only members who shared TDR mutations. Among clustered individuals, people with TDR were more likely to be in small clusters.

**Conclusion:** In a unique, statewide analysis of longitudinal trends in a densely-sampled HIV epidemic over 2004–2020, we found ongoing increases in TDR prevalence, to a high 26% by 2020, primarily, but not solely, driven by NNRTI-associated resistance, with impact on ART and evidence for transmissions within networks. Limited TDR to multi-class and pre-exposure prophylaxis (PrEP)-containing drugs is encouraging; however routine TDR surveillance and its integration with molecular epidemiology should continue, to improve and inform care and prevention interventions.

## 518 IMPACT OF NASH ON THE SURVIVAL OF PEOPLE LIVING WITH HIV

**Clinical:**

**Juan Macias**[1], Antonio Rivero-Juarez[2], Alejandro Gonzalez-Serna[1], Mario Frías[2], Marta Santos[1], Ignacio Perez-Valero[2], Anaïs Corma-Gomez[1], Antonio Rivero[2], Miguel Garcia-Deltoro[3], Luis M Real[1], Juan A. Pineda[1]

*[1]Hospital Universitario de Valme, Seville, Spain, [2]Hospital Universitario Reina Sofia, Cordoba, Spain, [3]Hospital General de Valencia, Valencia, Spain*

**Background:** Non-alcoholic fatty liver disease (NAFLD) is an increasing concern for PLWH. However, information on the impact of NAFLD on the prognosis of PLWH is lacking. Because of these, we investigated the influence of non-alcoholic steatohepatitis (NASH) on the overall mortality in PLWH.

**Methods:** PLWH followed in three Spanish centers were included in a prospective cohort at the date when a vibration-controlled transient elastography (VCTE) evaluation, including controlled attenuation parameter (CAP) measurement was conducted for the first time. Clinical visits were scheduled, at least, every 6 months. Survival data was recorded, and the causes of death were centrally monitored. The risk of all-cause of death were evaluated applying time-to-event analyses. NAFLD was defined as steatosis (CAP ≥248 dB/m) without any other liver disease. Cirrhosis was defined as liver stiffness measurement (LSM) ≥10.3 kPa for NAFDL (Wong. Hepatology 2010). The FibroScan-AST (FAST) score (Newsome. Lancet Gastroenterol Hepatol 2020), which includes AST, CAP and LSM was calculated.

**Results:** 1570 PLWH were included in the cohort and followed for a median (Q1-Q3) of 63 (22-100) months. There were 61 (3.4%) deaths. The main causes of death were: Liver-related, 22 (36%); cancer, 15 (25%); AIDS, 8 (13%); cardiovascular, 6 (9.8%); non-AIDS-related infections, 5 (8.2%); other, 5 (8.2%). Overall, cirrhosis was identified in 94 (14%) PLWH, and FAST score value was ≥0.67 in 156 (10%) PLWH. Among 614 PLWH without other concomitant liver diseases, NAFLD was observed in 248 (40%) of them. Steatosis was not associated with overall mortality. For PLWH with NAFLD, the higher LSM, the lower the probability of survival (Fig 1A). FAST score ≥0.67 was also associated with a lower likelihood of survival in PLWH with NAFLD (Fig 1B). After adjustment by variables related with survival, LSM was associated with increased all-cause mortality [adjusted hazard ratio (HR), by 1 kPa increase: 1.05; 95% confidence interval (95% CI): 1.01-1.09; p=0.047]. In a separate model and after adjustment for predictors of death, FAST score ≥0.67 was also related with a higher risk of death (Adjusted HR: 11.03; 95% CI: 2.6-49.8; p=0.001).

Similar results for LSM and FAST were found for the overall cohort (Fig 1C-1D).
**Conclusion:** Among PLWH, NAFLD, as a whole, is not associated with survival. However, when liver fibrosis coexists, the risk of death increases in parallel. Accordingly, both LSM and the FAST score are predictors of survival in this setting.

Fig 1A. NAFLD: Survival according to liver stiffness

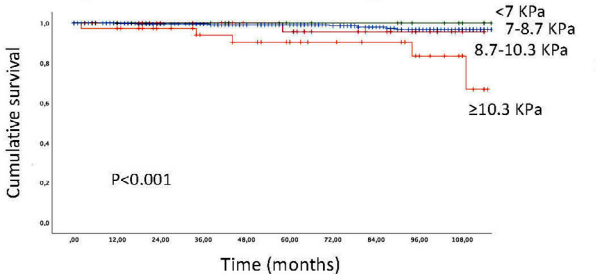
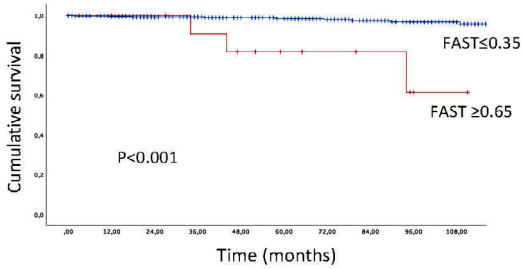



Fig 1B. NAFLD: Survival according to FAST score




## 519 NONINVASIVE PREDICTION OF HEPATIC DECOMPENSATION IN PATIENTS WITH HIV

New Investigator Scholar

**Amine Benmassaoud**[1], Juan Macias[2], Anaïs Corma-Gomez[2], Giovanni Guaraldi[3], Jovana Milic[3], Jürgen K. Rockstroh[4], Kathrin Van Bremen[4], Emmanuel Tsochatzis[5], Akhilesh Mulay[5], Jennifer Price[6], Lucy J. Garvey[7], Dana Kablawi[1], Juan A. Pineda[2], Victor De-Ledinghen[8], Giada Sebastiani[1]
*[1]McGill University Health Centre, Montreal, Canada, [2]Hospital Universitario de Valme, Seville, Spain, [3]University of Modena and Reggio Emilia, Modena, Italy, [4]Bonn University Hospital, Bonn, Germany, [5]Royal Free London NHS Foundation Trust, London, UK, [6]University of California San Francisco, San Francisco, CA, USA, [7]Imperial College Healthcare NHS Trust, London, UK, [8]Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France*

**Background:** People with HIV (PWH) are at high risk for compensated advanced chronic liver disease (cACLD) and hepatic decompensation. While non-invasive tools (NITs) such as liver stiffness measurement (LSM) by transient elastography are used to identify those at risk of hepatic decompensation, these remain not validated and potentially inaccurate in the setting of non-cirrhotic portal hypertension which can occur in PWH. We aimed to identify an optimal strategy to predict any liver event or death by comparing various NITs.
**Methods:** This was an international multicenter retrospective cohort study including PWH who underwent LSM. Participants were excluded if they had a previous hepatic decompensation or unreliable baseline LSM. Patients were stratified in four groups (Gr) based on thrombocytopenia (Plt≤150) and presence of cACLD (LSM≥10kPa): Gr1= LSM<10kPa, Plt>150; Gr2= LSM<10kPa, Plt≤150; Gr3= LSM≥10kPa, Plt>150; Gr4= LSM≥10kPa, Plt≤150. Incidence of any event (hepatic decompensation, hepatocellular carcinoma and death) was assessed. NITs evaluated included LSM, LSM to Plt (LPR), LSM-spleen diameter to Plt ratio (LSPS), and Portal Hypertension risk score (PHRS). NITs were assessed using area under the receiver operating curve (AUROC) analysis to predict any event and thresholds were selected based on Youden's index. Predictors of any event were assessed using Cox-regression analysis.
**Results:** We included a total of 1488 PWH (mean age 48.5 yrs, 76% males, mean duration of HIV infection 18.5 yrs, 26.5% HIV mono-infected, 64.9% co-infected with hepatitis C). When compared to Gr1, the incidence rate ratio of any liver event excluding death was 9.79 (95%CI 2.4-47.7) for Gr2, 17.22 (95%CI 5.9-73.3) for Gr3, and 44.79 (95%CI 16.7-183.1) for Gr4. Based on AUROC analysis, LSM [0.828 (95%CI 0.776-0.881)], LPR [0.831 (95%CI 0.784-0.878)], LSPS [0.832 (95%CI 0.785-0.884)], and PHRS [0.835 (95%CI 0.785-0.879)] all performed well to predict any event. Using separate models for each NIT using their respective cutoffs based on Youden's index, LSM, LPR, LSPS, and PHRS remained independent predictors of any event after adjustments (Table 1).
**Conclusion:** In PWH, thrombocytopenia identifies patients at risk of liver events even in the absence of cACLD, likely due to non-cirrhotic portal hypertension. Although all NITs performed similarly well, the use of NITs combining Plt and spleen diameter provides a more global assessment of a patient's risk of any event.

**Table 1** – Multivariate Cox regression analysis for development of hepatic decompensation, hepatocellular carcinoma or death.

| Variables | HR (95%CI) | p-value |
|---|---|---|
| Model 1 | | |
| **LSM above 15.9kPa** | **4.087 (95%CI 1.955-8.543)** | **<0.001** |
| Gender, ref male | 0.895 (95%CI 0.463-1.727) | 0.740 |
| Duration of HIV, per year | 1.009 (95%CI 0.976-1.042) | 0.601 |
| **Spleen diameter, per cm** | **1.102 (95%CI 1.006-1.207)** | **0.037** |
| Platelets, per unit | 0.998 (95% CI 0.993-1.004) | 0.541 |
| Co-infection status, ref HIV-monoinfection | 1.384 (95%CI 0.584-3.280) | 0.460 |
| Model 2 | | |
| **LPR above 5.49** | **7.279 (2.585-20.501)** | **<0.001** |
| Gender, ref male | 0.813 (0.419-1.576) | 0.539 |
| Duration of HIV, per year | 1.000 (0.968-1.033) | 0.983 |
| **Spleen diameter, per cm** | **1.113 (1.019-1.215)** | **0.017** |
| Co-infection status, ref HIV-monoinfection | 1.257 (0.560-2.821) | 0.579 |
| Model 3 | | |
| **LSPS above 0.60** | **11.969 (4.003-35.789)** | **<0.001** |
| Gender, ref male | 0.792 (0.411-1.529) | 0.488 |
| Duration of HIV, per year | 1.001 (0.970-1.034) | 0.934 |
| Co-infection status, ref HIV-monoinfection | 1.367 (0.615-3.040) | 0.443 |
| Model 4 | | |
| **PHRS above 0.54** | **5.268 (2.569-10.801)** | **<0.001** |
| Duration of HIV, per year | 1.008 (0.975-1.041) | 0.654 |
| Co-infection status, ref HIV-monoinfection | 1.715 (0.766-3.841) | 0.190 |

## 520 NAFLD IS COMMON AND ASSOCIATED WITH CARDIOVASCULAR RISK IN REPRIEVE PARTICIPANTS

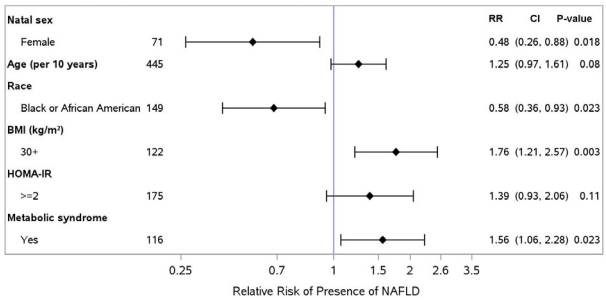
**Carl J. Fichtenbaum**[1], Heather J. Ribaudo[2], Jana Taron[3], Jorge T. Leon-Cruz[2], Netanya S. Utay[4], Ken Ho[5], Annie Luetkemeyer[6], Shobha Swaminathan[7], Carrie Johnston[8], Evelynne S. Fulda[9], Emma Kileel[10], Michael T. Lu[9], Steven Grinspoon[9], Jordan Lake[11]
*[1]University of Cincinnati, Cincinnati, OH, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University Hospital Freiburg, Freiburg, Germany, [4]University of Texas Southwestern, Dallas, TX, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]University of California San Francisco, San Francisco, CA, USA, [7]Rutgers Robert Wood Johnson Medical School, Piscataway, NJ, USA, [8]Weill Cornell Medicine, New York, NY, USA, [9]Massachusetts General Hospital, Boston, MA, USA, [10]Boston University, Boston, MA, USA, [11]University of Texas at Houston, Houston, TX, USA*

**Background:** Non-alcoholic fatty liver disease (NAFLD) is a common problem in persons with HIV (PWH). NAFLD is associated elevated cardiovascular disease (CVD) risk. We present baseline data on the prevalence and cardiometabolic characteristics of NAFLD among REPRIEVE participants who underwent Computed Tomography (CT).
**Methods:** The REPRIEVE Mechanistic substudy is embedded within an international primary CVD prevention RCT of pitavastatin calcium vs. placebo among 7,770 PWH ages 40-75 years on antiretroviral therapy (ART). A subset of 655 U.S. participants had non-contrast CT with measurement of hepatic steatosis defined as a mean hepatic attenuation <40 HU or liver/spleen ratio <1.0. NAFLD was defined as steatosis in the absence of frequent alcohol use. The prevalence of NAFLD was compared by demographic, cardiometabolic and HIV-specific parameters. Distributions of immune activation/inflammatory indices data were compared among those with or without NAFLD. Analyses used log binomial regression and Wilcoxon tests.
**Results:** Among 655 PWH: median age was 51 years, 17% natal female sex, 44% black race, median BMI 27 kg/m$_2$, median CD4 count 606 c/mm$_3$ and 98% with HIV VL <400 copies/mL. NAFLD prevalence was 20% (97/477 without frequent alcohol use). ALT was abnormally ↑ in those with NAFLD (45% vs. 25%, P<0.001). NAFLD was more prevalent with male sex, older age, non-black race (Figure). ASCVD risk score was higher in those with NAFLD (median 5.8% vs.

4.3%, P=0.002). Obesity, metabolic syndrome, elevated waist circumference, reduced HDL and elevated triglycerides, were all associated with NAFLD in unadjusted analyses (P<0.005); these effects were explained by obesity, metabolic syndrome and elevated HOMA-IR (Figure). NAFLD was associated with higher levels of LpPLA-2 (144 vs. 130 ng/ml, P=0.013) and hsCRP (2.2 vs. 1.6 mg/L, P=0.013). HIV-specific characteristics, ART and other circulating markers of immune activation/inflammation (IL-6, sCD163, MCP-1, sCD14 and D-dimer) were not associated with NAFLD.

**Conclusion:** In this cohort with controlled HIV, high CD4 counts, and low to moderate cardiovascular risk, NAFLD (20%) was common including 45% with clinically relevant ↑ in ALT. NAFLD was associated with select indices of inflammation and metabolic disturbances but not HIV or ART. NAFLD was more prevalent with male sex, older age, non-black race, elevated BMI and metabolic syndrome. Elevated LpPLA-2 and hsCRP levels suggest a correlation between NAFLD and cardiovascular risk in PWH.

**Figure: Adjusted Model of Non-Alcoholic Fatty Liver Disease**




## 521 FROM NAFLD TO MAFLD: IMPLICATIONS OF CHANGE IN TERMINOLOGY IN PWH

**Giovanni Guaraldi**[1], Jovana Milic[1], Stefano Renzetti[2], Federico Motta[1], Licia Gozzi[1], Adriana Cervo[3], Giulia Burastero[3], Vittorio Iadisernia[3], Bertrand Lebouché[4], Alshaima Alhinai[4], Marc Deschenes[4], Paolo Raggi[5], Stefano Calza[2], Cristina Mussini[1], Giada Sebastiani[4]

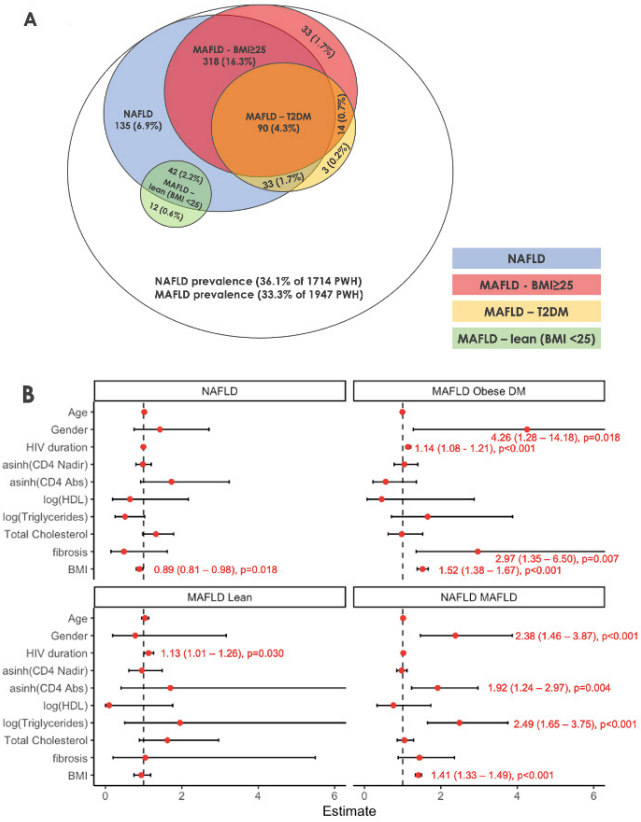
*[1]University of Modena and Reggio Emilia, Modena, Italy, [2]University of Brescia, Brescia, Italy, [3]Azienda Ospedaliera Universitaria Policlinico di Modena, Modena, Italy, [4]McGill University, Montreal, Canada, [5]University of Alberta, Edmonton, Canada*

**Background:** Metabolic associated fatty liver disease (MAFLD) has been recently proposed as a new concept to describe nonalcoholic fatty liver disease (NAFLD), based on positive diagnostic criteria rather than exclusionary ones. The ongoing debate regarding NAFLD/MAFLD construct has not yet reached HIV arena. Our objective was to characterize MAFLD in comparison to NAFLD and to determine prevalence and predictors of both conditions in people with HIV (PWH).

**Methods:** This was a cross-sectional study of two prospective cohorts comprising PWH on stable ART, that were screened for fatty liver disease (FLD) defined as controlled attenuation parameter of ≥248 dB/m by transient elastography. NAFLD was defined as FLD in absence of significant alcohol intake and HBV or HCV co-infection. MAFLD was defined as the presence of FLD and at least one of the following criteria: 1) overweight/obesity; 2) diabetes; or 3) lean FLD (BMI<25 kg/m$_2$) with at least two immune-metabolic alterations [Eslam M. JHepatol.2020;73(1):202-209]. Significant liver fibrosis was defined as liver stiffness ≥7.1 kPa. Predictors for both conditions were explored in logistic regression.

**Results:** We included 1947 PWH (mean age 54 years, 74% males, median HIV duration 21 years, median current CD4 703, 98% with undetectable HIV viral load, current ART exposure to InSTI 53%, PI/c 25%, 32% NNRTI). Prevalence of overweight/obesity and diabetes was 23.4% and 49.5%. NAFLD was diagnosed in 618/1714 (36.1 %) PWH, after excluding PWH with significant alcohol intake (1.8%), HBV (1.2%), HCV (9.2%). MAFLD was diagnosed in 648 (33.3%) PWH. Prevalence of significant liver fibrosis differed across the groups: 9.9% in no NAFLD-no MAFLD, 9.3% in NAFLD only, 26.5% in NAFLD/MAFLD overlap, 48% in MAFLD with diabetes and overweight/obesity, and 16.7% in lean MAFLD. Figure 1A depicts proportions of PWH with NAFLD, MAFLD and NAFLD/MAFLD overlap. Figure 1B shows that male sex, higher CD4, triglycerides and BMI were associated with NAFLD/MAFLD. Significant liver fibrosis was associated with MAFLD with diabetes and overweight/obesity.

**Conclusion:** PWH displayed a substantial overlap between NAFLD and MAFLD, but those with MAFLD and diabetes or overweight/obesity had higher probability of significant liver fibrosis. HIV-related and metabolic variables were independent predictors of NAFLD/MAFLD. Change of terminology may help to prioritize PWH requiring surveillance and interventions for the management of FLD and associated liver fibrosis.




## 522 THE PATHWAY OF NAFLD VS MAFLD TOWARD SIGNIFICANT FIBROSIS

New Investigator Scholar

**Jovana Milic**[1], Stefano Renzetti[2], Federico Motta[1], Licia Gozzi[1], Giulia Besutti[3], Giulia Burastero[4], Vittorio Iadisernia[4], Bertrand Lebouché[5], Alshaima Alhinai[5], Marc Deschenes[5], Stefano Calza[2], Cristina Mussini[1], Giada Sebastiani[5], Giovanni Guaraldi[1]

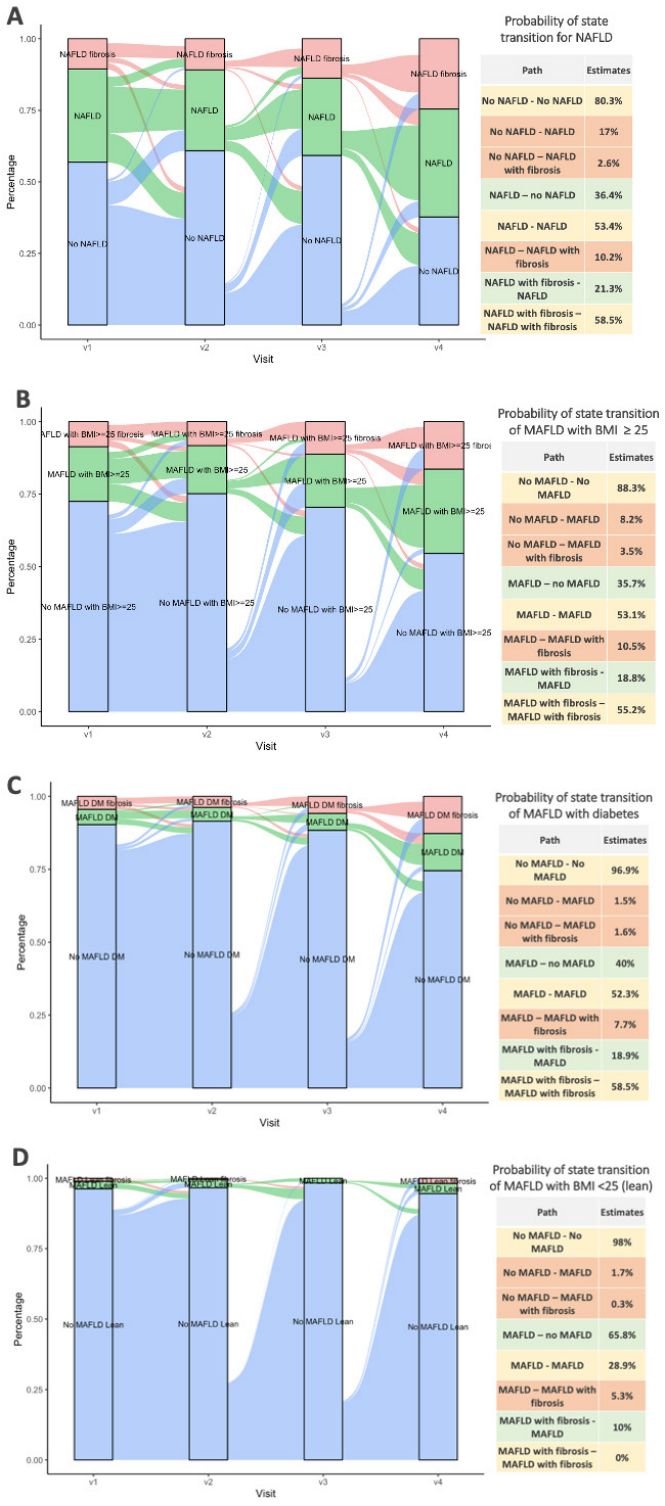
*[1]University of Modena and Reggio Emilia, Modena, Italy, [2]University of Brescia, Brescia, Italy, [3]Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Italy, [4]Azienda Ospedaliera Universitaria Policlinico di Modena, Modena, Italy, [5]McGill University, Montreal, Canada*

**Background:** The ongoing debate regarding nonalcoholic fatty liver disease (NAFLD)/metabolic-associated fatty liver disease (MAFLD) should consider risk of progression of fatty liver disease (FLD). We aimed to describe transition of NAFLD and MAFLD states towards significant fibrosis in people with HIV (PWH).

**Methods:** This was a longitudinal study of two prospective cohorts of PWH on stable antiretroviral therapy. FLD was assessed at least twice with controlled attenuation parameter (CAP ≥248 dB/m) by transient elastography. NAFLD was defined as FLD in absence of significant alcohol intake or HBV or HCV co-infections. MAFLD was defined as the presence of FLD and at least one criteria: 1) BMI≥25 kg/m$_2$; 2) diabetes; or 3) lean (BMI<25 kg/m$_2$) with at least two immune-metabolic alterations [Eslam M. JHepatol.2020;73(1):202-209]. Significant liver fibrosis was defined as liver stiffness ≥7.1 kPa. A continuous-time multi-state Markov model was used to describe the process in which a study patient moved through a series of states allowing joint analysis of care length, incidence of FLD or fibrosis progression or reversion. The probabilities to switch from one state to another were modelled according to an exponential distribution for time-to-event data, considering censored follow-up times. The events were the transitions between the states. The analyses were performed separately for NAFLD and three MAFLD categories in which minimum two and maximum four assessments for FLD were considered.

**Results:** A total of 888 PWH were screened for FLD, with a mean follow-up of 2 years, mean age 54.4 years, 77% males. At the first visit, after excluding PWH

with alcohol intake and viral co-infections, prevalence of NAFLD was 42.9% (285/664), while the overall prevalence of the MAFLD was 34.3% (305/888). In detail, MAFLD with BMI≥25 kg/m$_2$ was present in 244 (27.5%), MAFLD with diabetes in 86 (9.7%) and lean MAFLD in 33 (3.7%). Figure 1 shows alluvial plots of state transitions in NAFLD (panel A) and in MAFLD with BMI≥25 kg/m$_2$ (Panel B), with diabetes (Panel C) and lean MAFLD (Panel D). Each panel is accompanied by table that summarizes probabilities to move from one state to another.
**Conclusion:** Use of Markov models depicts dynamic changes of FLD with or without fibrosis over time. The highest risk of liver fibrosis progression was observed in PWH with MAFLD with BMI >25. MAFLD categories offer the possibility to stratify PWH at highest risk of hepatic and extra-hepatic adverse outcomes.




## 523 HIGH INCIDENCE RATE OF CT-MEASURED NAFLD IN MEN WITH AND WITHOUT HIV INFECTION

**Jennifer Price**[1], Gayle Springer[2], Eric C. Seaberg[2], Matthew Budoff[3], Susan L. Koletar[4], Claudia Hawkins[5], Mallory Witt[6], Wendy Post[7], Chloe L. Thio[7]
*[1]University of California San Francisco, San Francisco, CA, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]Harbor–University of California Los Angeles Medical Center, Torrance, CA, USA, [4]The Ohio State University, Columbus, OH, USA, [5]Northwestern University, Chicago, IL, USA, [6]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA, [7]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** Nonalcoholic fatty liver disease (NAFLD) can progress to cirrhosis, hepatocellular carcinoma, and end-stage liver failure. Although NAFLD has become a major cause of liver disease including among persons with HIV (PWH), few studies have examined NAFLD incidence in PWH. We aimed to determine NAFLD incidence among PWH and persons without HIV (PWOH) within the Multicenter AIDS Cohort Study (MACS), a prospective cohort of men who have sex with men.
**Methods:** MACS participants were included if they had two non-contrast cardiac CT scans with complete visualization of the liver and spleen, consumed on average <3 alcoholic drinks daily and had stored cells for DNA extraction for PNPLA3 testing. Baseline CT scans were performed from 2010-2013 and follow-up scans from 2015-2017. Incident NAFLD was defined as men without hepatic steatosis at baseline who had steatosis (liver/spleen Hounsfield unit ratio <1.0) at follow-up. Visceral adipose tissue (VAT) was measured in one axial image obtained between the 4th and 5th lumbar vertebrae, and the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using 8-hour fasting insulin and glucose values. Incidence rates (IRs) were calculated using a person-years (PYs) analysis. Generalized linear regression models were used to determine factors associated with incident NAFLD.
**Results:** In total, 268 men were eligible: 173 men with HIV (MWH) and 95 men without HIV (MWOH), with median age 57 years (IQR 53-62), 53% White and 35% Black. Median time between CT scans was 4.5 years (IQR 3.8-5.0). Thirty men had incident NAFLD (11.1%), with an overall IR of 2.53 /100 PYs (95% CI 1.77, 3.62): IR 2.42/100 PYs (95% CI 1.55, 3.80) for MWH and 2.73/100 PY (95% CI 1.51, 4.93) for MWOH (p=0.75). The IRs for lean (BMI<25 kg/m$_2$) and non-lean (BMI≥25 kg/m$_2$) men were 1.25/100 PYs (95% CI 0.56, 2.77) and 3.58/100 PYs (95% CI 2.31, 5.56), respectively (p=0.02). In multivariable analysis, higher abdominal VAT was associated with increased risk of NAFLD (Table).
**Conclusion:** Visceral adiposity, but not HIV infection, was associated with incident NAFLD as determined by serial non-contrast CT scans. Although MWH were not at higher risk of NAFLD than MWOH, the high observed IR of NAFLD relative to previously published IRs of hepatitis B and C among MWH in the same cohort suggests that NAFLD will continue to increase as cause of liver disease in PWH.

**Table. Associations with incident NAFLD (N=268)***

| | IRR (95% CI) | p-value |
|---|---|---|
| Infection Status | | |
| PWH (ref=HIV seronegative) | 0.77 (0.33,1.77) | 0.53 |
| Chronic hepatitis B virus | 2.45 (0.53,11.27) | 0.25 |
| Chronic hepatitis C virus | 0.43 (0.06,3.31) | 0.41 |
| PNPLA CG/GG (ref=CC) | 1.53 (0.73,3.20) | 0.27 |
| Abdominal VAT (per 10 cm$^2$) | 1.06 (1.01,1.11) | 0.02 |
| ln(HOMA-IR) | 1.31 (0.60,2.86) | 0.50 |

*Adjusted for the variables listed and age and MACS site
Abbreviations: NH, non-Hispanic; PWH, persons with HIV; PNPLA3, patatin-like phospholipase domain-containing 3 gene (rs738409); VAT, visceral adipose tissue; HOMA-IR, homeostatic model assessment of insulin resistance

## 524 DETERMINANTS OF LIVER STEATOSIS IN PEOPLE LIVING WITH HIV ON ANTIRETROVIRAL THERAPY

New Investigator Scholar

**Carlotta Riebensahm**[1], Annalisa Berzigotti[1], Bernard Surial[1], Huldrych F. Günthard[2], Philip Tarr[3], Hansjakob Furrer[1], Andri Rauch[1], Gilles Wandeler[1]
*[1]Bern University Hospital, University of Bern, Switzerland, Bern, Switzerland, [2]University Hospital Zurich, University of Zurich, Zurich, Switzerland, [3]Kantonsspital Bruderholz, University of Basel, Basel, Switzerland*

**Background:** Given the impact of new antiretroviral drugs, including integrase strand inhibitors (InSTI) and tenofovir alafenamide (TAF), on weight and other metabolic parameters, their potential contribution to the development of liver steatosis is of concern. We investigated the determinants of liver steatosis in patients on antiretroviral therapy (ART) in a single site of the Swiss HIV Cohorts Study (SHCS).
**Methods:** Between November 2019 and August 2021, we enrolled consecutive persons living with HIV (PLWH) at Bern University Hospital. Individuals with active or past viral hepatitis co-infection and pregnant women were excluded. Demographic, clinical and laboratory data, as well as changes in ART regimens were recorded at registration, and every six months thereafter. All participants were invited to undergo liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) using transient elastography (TE). We used multivariable logistic regression to explore factors associated with steatosis.
**Results:** Of 645 eligible individuals, 416 (64.5%) agreed to participate and had a reliable TE measurement. Their median age was 51 years (interquartile range [IQR] 43-59), 113 (27.2%) were female, 305 (73.3%) were Caucasian, and 212 (51.0%) overweight (BMI ≥ 25). At time of LSM, participants had been on ART for a median time of 13 (IQR 6-19) years, 279 (67.1%) had been exposed to InSTI and 229 (55.1%) to TAF. S1-S3 liver steatosis (CAP ≥ 248dB/m) was present in 212 (51.0%) participants, of whom 139 (33.4%) had severe steatosis (S3, CAP ≥ 280dB/m). Among individuals with S1-S3 steatosis, 11 (5.2%) had a LSM compatible with significant fibrosis or cirrhosis. In multivariable analyses, BMI ≥25kg/$m_2$ (adjusted odds ratio, 5.78; 95% confidence interval, 3.59-9.32), age ≥50 years (1.88, 1.14-3.09), and European origin (3.11, 1.67-5.79) were strongly associated with liver steatosis. We did not find any evidence of an association between the use of InSTI and liver steatosis (0.87, 0.54-1.41), whereas participants on a TAF-containing regimen were more likely to have liver steatosis than those not exposed to TAF (1.66, 1.05-2.62). The latter association did not depend on the time spent on TAF.
**Conclusion:** Our data show a high prevalence of liver steatosis among PLWH on ART in Switzerland. In addition to well-established risk factors such as age, ethnicity and obesity, the use of TAF was significantly associated with hepatic steatosis.

## 525 CANNABIS USE AND HEPATIC STEATOSIS BY MRI-PDFF

**Janet Diaz-Martinez**[1], Javier A. Tamargo[1], Ivan Delgado-Enciso[2], Richard Ehman[3], Jun Chen[3], Kenneth E. Sherman[4], Leslie Seminario[4], Jupshy Jasmin[1], Marianna K. Baum[1]
*[1]Florida International University, Miami, FL, USA, [2]University of Colima, Colima, Mexico, [3]Mayo Clinic, Rochester, MN, USA, [4]University of Cincinnati, Cincinnati, OH, USA*

**Background:** There is conflicting evidence regarding the impact of cannabis use on liver steatosis in patients affected by HIV and HCV infections. We therefore assessed the relationship between the use of cannabis and hepatic steatosis in a cohort of people living with and without HIV and HCV.
**Methods:** Cross-sectional analysis of the Miami Adult Studies on HIV (MASH) cohort. The use of cannabis in the past 30 days was self-reported. Hepatic steatosis (>5%) was assessed with magnetic resonance-determined proton density fat-fraction (MRI-PDFF).
**Results:** There were 467 participants of whom 50.3% were HIV-infected on antiretroviral therapy and 26.1% were HCV-infected. Sixty-eight participants (14.6%) had hepatic steatosis. Multivariate logistic regression showed that BMI (kg/$m_2$; adjusted odds ratio [aOR] 1.11, 95% CI 1.06-1.17, P <0.001) and cannabis use (aOR 0.48, 95% CI 0.26-0.91, P=0.024) were significant independent predictors of hepatic steatosis after adjustment for covariates found significant in univariate analyses. Cannabis use reduces the risk of hepatic steatosis in both obese (BMI >30 kg/$m_2$; relative risk [RR] 0.47, 95% CI 0.22-0.98, P=0.044) and non-obese (RR 0.37, CI95% 0.14-0.94, P=0.038). Bivariate logistic regression analysis stratified by HIV/HCV status was used to study the relationship of BMI and cannabis with hepatic steatosis in HIV and/or HCV. The use of cannabis was associated with lower odds for hepatic steatosis in the HIV/HCV-uninfected (odds ratio [OR] 0.18, 95% CI 0.05-0.64, P=0.008) and HIV mono-infected (OR 0.40, 95% CI 0.16-0.99, P=0.047) groups, but not in HCV-infected groups (Table). BMI increased the risk of liver steatosis in all groups except in the HCV mono-infected (Table).
**Conclusion:** Based on our results, the use of cannabis may reduce the risk of hepatic steatosis in HIV/HCV-uninfected and HIV mono-infected, but not in HCV-infected individuals. The analyses showed this association both in obese and non-obese participants. These findings add to a growing body of evidence that is not entirely consistent on the impact of cannabis use on hepatic steatosis. Studies are needed to elucidate lifestyle and biologic mechanisms for the beneficial effect of cannabis use observed in this study.

**Bivariate logistic regression for hepatic steatosis (> 5% fat) stratified by HIV/HCV status**

| | Adjusted* | 95% CI | | | Adjusted | 95% CI | | |
|---|---|---|---|---|---|---|---|---|
| Covariate | OR | Lower | Upper | P | OR | Lower | Upper | P |
| | HIV/HCV uninfected (n=168) | | | | HIV mono-infected (n=180) | | | |
| BMI, kg/$m^2$ | 1.08 | 1.01 | 1.16 | **0.036** | 1.16 | 1.07 | 1.25 | **<0.001** |
| Cannabis | 0.18 | 0.05 | 0.64 | **0.008** | 0.40 | 0.16 | 0.98 | **0.047** |
| | HCV mono-infected (n=64) | | | | HIV/HCV co-infected (n=58) | | | |
| BMI, kg/$m^2$ | 1.03 | 0.85 | 1.25 | 0.730 | 1.14 | 1.01 | 1.29 | **0.041** |
| Cannabis | 0.99 | 0.13 | 7.49 | 0.989 | 1.55 | 0.36 | 6.56 | 0.555 |

## 526 METABOLIC-ASSOCIATED FATTY LIVER DISEASE AND ITS ASSOCIATION WITH EPICARDIAL FAT

**Win Min Han**[1], Tanakorn Apornpong[1], Sasiwimol Ubolyam[1], Stephen J. Kerr[1], Anchalee Avihingsanon[1]
*[1]HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand*

**Background:** Increasing evidence suggests fatty liver disease and metabolic conditions fall along a spectrum. An entity of metabolic associated fatty liver disease (MAFLD) has been recently proposed. We investigated the prevalence and factors associated with MAFLD, and associations with cardiovascular disease (CVD) in older people living with HIV(PWH).
**Methods:** We conducted a cross-sectional assessment of CVD risk (epicardial fat tissue, coronary calcium score (CAC) and 10-year atherosclerotic CVD score (ASCVD)) in participants aged >50 years from March 2018 to September 2019, in an aging HIV cohort in Bangkok, Thailand. PWH with significant alcohol consumption and hepatitis infections were excluded. Transient elastrography was performed, and non-alcohol fatty liver disease (NAFLD) was defined as controlled attenuation parameter (CAP) ≥248 dB/m. MAFLD diagnosis was based on 2020 International Consensus criteria. The discriminatory ability of MAFLD and NAFLD to identify higher epicardial fat volume (defined as >median value of 100 cm...3) was assessed using the area under the receiver operating characteristic (AROC) curve.
**Results:** A total of 319 PWH (37% female) with median (interquartile range [IQR]) age 54 (52-60) years, and CD4 of 613 (467-804) cells/mm...3 and were included. Most (98%) were virally suppressed. MAFLD and NAFLD prevalence was 35% and 38%, respectively. Epicardial fat volume was significantly higher in PWH with MALFD than those without MAFLD (mean ±SD, 113.6 ±38.7 vs. 98.9 ±39.7 cm3, p<0.001). Liver stiffness (5.8 [4.8-7.3) vs. 5.4 [4.4-6.8] kPa, p=0.11), 10-year ASCVD risk (6.7% [3.8-14.0] vs. 5.9% [2.8-11.4], p=0.09) and CAC were comparable between PWH by MAFLD status. In a multivariable model, higher albumin (odds ratio [OR]=1.99, 95%CI 1.21-3.29), epicardial fat volume >100 cm...3 (OR=2.41, 95%CI 1.42-4.09), and CD4/CD8 ratio >1 (OR=0.55, 95%CI 0.32-0.97), were significantly associated with MAFLD. In a model adjusted for confounders, epicardial fat volume >100 cm3 showed similar discriminative ability for both MAFLD (AROC: 0.699, 95%CI 0.642-0.757) and NAFLD (AROC: 0.698, 95%CI 0.641-0.755, p=0.89).
**Conclusion:** In older PWH, >33% met criteria for MAFLD, so routine screening of metabolic disease in this population remains highly relevant. The association of MAFLD with epicardial fat tissue is consistent with previous evidence suggesting CVD risk is higher in those with fatty liver disease.

## 527 NONOBESE NAFLD IS ASSOCIATED WITH HIGHER sCD14 CONCENTRATIONS IN ADULTS WITH HIV

**Jordan Lake**[1], Han Feng[1], Hongyu Miao[1], Paula Debroy[1], Anoma Somasunderam[1], Netanya S. Utay[1]
*[1]University of Texas at Houston, Houston, TX, USA*

**Background:** Hepatic steatosis is highly prevalent in people living with HIV (PLWH). Additionally, non-obese (BMI <30 kg/$m_2$), non-alcoholic fatty liver disease (NAFLD) may be more frequent in PLWH than the general population, but etiology and risk factors are incompletely understood. Soluble CD14 (sCD14) is a marker of monocyte/Kupffer cell activation that is associated with (obese) NAFLD disease severity. We sought to understand factors associated with hepatic steatosis and non-obese NAFLD in a multi-ethnic cohort of PLWH.
**Methods:** In this cross-sectional, observational, single center study in Houston, TX (2017-2020), adult PLWH were approached at random and offered screening for hepatic steatosis by FibroScan® controlled attenuation parameter (CAP) measurement. Biomarkers associated with NAFLD physiology in the general

population were measured centrally by ELISA. Multivariable regression modeling explored factors associated with hepatic steatosis (all participants) and the subset of PLWH with NAFLD (no heavy alcohol or viral hepatitis).
**Results:** Participants (n=194) were 95% non-white, 22% cisgender female, 34% transgender female, and had median age 49 years, time with HIV 15 years and time on ART 11 years; 5% had heavy alcohol intake, and 11% chronic HBV or HCV. Using CAP cutoffs of 248 and 260 dB/m, 58% of the cohort had any and 46% had moderate or greater hepatic steatosis, respectively. 41% of those with steatosis were non-obese. In multivariable analysis, Hispanic ethnicity and higher BMI and sCD14 concentrations were independently associated with hepatic steatosis (CAP ≥260 dB/m). In models assessing associations with non-obese steatosis and non-obese NAFLD, BMI was replaced by current smoking and hypertension, respectively. Changing the CAP cutoff to be more or less inclusive did not substantially change model results, with higher sCD14 levels consistently associated with steatosis prevalence. Additionally, sCD14 concentrations were higher among persons with non-obese NAFLD than obese NAFLD and non-NAFLD PLWH.
**Conclusion:** In this cohort of adult PLWH on contemporary ART, hepatic steatosis was common. Non-obese steatosis was prevalent in 20% of the cohort, a rate 5 times higher than the US general population. Higher sCD14 concentrations were associated with steatosis/NAFLD in obese and non-obese PLWH, but sCD14 concentrations were the highest among PLWH with non-obese NAFLD. The physiology of non-obese NAFLD in PLWH demands further exploration.

## 528 EFFICACY & SAFETY OF RAVIDASVIR + SOFOSBUVIR IN HEPATITIS C: STORM-C-1 FINAL RESULTS




**Soek-Siam Tan**[1], Sombat Thanprasertsuk[2], Satawat Thongsawat[3], Nicolas Salvadori[4], Caroline Menétrey[5]
*[1]Selayang Hospital, Selayang, Malaysia, [2]Department of Disease Control, Ministry of Public Health, Bangkok, Thailand, [3]Chiang Mai University, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand, [4]Chiang Mai University, Faculty of Associated Medical Sciences, Chiang Mai, Thailand, [5]Drugs for Neglected Diseases Initiative, Geneva, Switzerland*

**Background:** Affordable direct-acting antivirals are urgently needed to treat hepatitis C virus (HCV) infection in low and middle-income countries. STORM-C-1 aimed to assess the efficacy and safety of ravidasvir plus sofosbuvir in adults chronically infected with HCV, with or without HIV coinfection.
**Methods:** STORM-C-1 was a two-stage, open-label, Phase II/III single-arm clinical trial conducted in 13 public hospitals in Malaysia and Thailand. Participants with HCV, aged 18–69 years, without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh class A), were eligible to participate, regardless of HCV genotype, HIV infection status or previous interferon-based HCV treatment. Once daily ravidasvir (200 mg) and sofosbuvir (400 mg) were prescribed for 12 weeks for participants without cirrhosis or 24 weeks for those with cirrhosis. The primary endpoint was sustained virological response at 12 weeks after treatment (SVR12; defined as HCV RNA<lloq).< div="">
**Results:** Between September 2016, and September 2020, 603 participants were enrolled in STORM-C-1. Of these, 296 (49%) had genotype 3 infection, 162 (27%) had genotype 1a, 81 (13%) had genotype 1b, 61 (10%) had genotype 6 and 3 (<1%) had genotype 2. 238 (39%) had compensated cirrhosis, 192 (32%) had HIV co-infection, and 120 (20%) had received previous interferon-based treatment. SVR12 was achieved by 583/602 (96.8%; 95% CI 95.1- 98.1) participants. Results were comparable for difficult to treat subgroups: 230/238 (96.6%; 95% CI 93.5-98.5) for participants with cirrhosis; 289/296 (97.6%; 95% CI 95.2-99.0) with genotype 3 infection, and 186/192 (96.9%; 95% CI 93.3 to 98.8) with HIV co-infection. 70 Grade 3/4 treatment emergent adverse events occurred in 35 participants; of these, 9 in 5 participants were related to study treatment. There were 42 treatment emergent serious adverse events in 36 participants; only 1 (acute kidney injury) was assessed as possibly related to study treatment (sofosbuvir) by the investigator. Three deaths were reported, occurring after the 24-week post-treatment visit, not related to study treatment. There were no significant drug-drug interactions requiring switching of anti-retroviral therapies.
**Conclusion:** Ravidasvir with sofosbuvir is well tolerated with excellent safety and efficacy in HCV infection, including difficult to treat populations, making it suitable for implementation in public health settings.

## 529 TREATMENT WITH SOF/VEL/VOX IN HIV/HCV-COINFECTED PATIENTS PREVIOUSLY EXPOSED TO DAAs

**Luz Martin Carbonero**[1], Angela Gil-Martin[2], Teresa Aldámiz-Echevarría[3], Vicente Estrada[4], Carlos Barros[5], Rebeca Font[6], Pablo Ryan[7], Carmen Quereda[8], Beatriz Alvarez[9], Rafael Mican[10], Juan Berenguer[3], Jorge Vergas[4], Maria Luisa Montes[1], Juan C. Lopez[3]
*[1]La Paz University Hospital, Madrid, Spain, [2]Subdireccion General de Farmacia, Madrid, Spain, [3]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [4]Hospital Universitario Clínico San Carlos, Madrid, Spain, [5]Hospital Universitario de Móstoles, Madrid, Spain, [6]Hospital Universitario 12 de Octubre, Madrid, Spain, [7]Hospital Universitario Infanta Leonor, Madrid, Spain, [8]Hospital Ramón y Cajal, Madrid, Spain, [9]Fundacion Jimenez Diaz, Madrid, Spain, [10]Hospital La Paz Institute for Health Research, Madrid, Spain*

**Background:** Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is a pan-genotypic direct active antiviral (DAA) regimen approved for patients who have previously failed anti-HCV treatment with other DAAs. Little is known about the effectiveness of this regimen in HIV/HCV coinfected patients. We evaluated the effectiveness and safety of SOF/VEL/VOX in a prospective registry of coinfected patients treated with DAAs.
**Methods:** For this study, we selected coinfected patients who started treatment with SOF/VEL/VOX and recorded in Madrid-CoRE, a compulsory prospective registry of coinfected patients receiving all-oral DAAs in the Madrid Regional Health Service hospitals (Hepatology 2017; 66:344). The planned treatment duration was 12 weeks. We assessed sustained virologic response (SVR) at 12 weeks by intention-to-treat (ITT) and by per-protocol analysis (PP) in which patients with no response data or discontinuations were excluded for the analysis.
**Results:** A total of 56 patients met the inclusion criteria. The median (IQR) age was 51.9 (47-7-54.5) years, 92.9% were men, and 17.9% had cirrhosis. The genotype distribution was: G1, 67.8%; G3, 12.5%; G4, 16.1%; Other/mixed/unknown: 4.6%. The number of previous DAAs regimens was one in 76.5%, 2 in 15.5%, and three or more in 7.8%. The type of previous regimens included sofosbuvir/ledipasvir in 50% patients, ombitasvir/paritaprevir/ritonavir plus dasabuvir in 9.4%, sofosbuvir plus daclatasvir in 9.4%, elbasvir/grazoprevir in 9.4%, glecaprevir/pibrentasvir in 9.4% and 13.4% other regimens. SVR rates were 80.4% (95% CI, 68.2%-89.7%) by ITT and 95.7% (95% CI, 85.7%-98.8%) by PP analysis. A total of 9 patients were not included in the PP analysis (2 discontinuations and 7 without data). Liver cirrhosis and genotype did not influence treatment response (SVR by ITT 90% for cirrhosis and 85.8% for G3).
**Conclusion:** Our findings suggest that SOF/VEL/VOX is a highly effective regimen for treatment of coinfected patients previously failing to DAA regimens, across all genotypes and in the presence of cirrhosis.

## 530 ADHERENCE IN THE ACTG A5360 HCV MINIMAL MONITORING (MINMON) TRIAL

**Leonard Sowah**[1], Laura M. Smeaton[2], Irena Brates[2], Debika Bhattacharya[3], Benjamin Linas[4], Bruce Kreter[5], Sandra Wagner-Cardoso[6], Sunil S. Solomon[7], Mark S. Sulkowski[7], Gregory K. Robbins[8]
*[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]Boston Medical Center, Boston, MA, USA, [5]Gilead Sciences, Inc, Foster City, CA, USA, [6]Institute Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, [7]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [8]Massachusetts General Hospital, Boston, MA, USA*

**Background:** The association of adherence with treatment outcomes and correlates of non-adherence among persons receiving DAA therapy for HCV are limited. ACTG A5360 (MINMON) was a single-arm, open-label, multinational trial to evaluate the safety and efficacy of 12 weeks of Sofosbuvir/Velpatasvir (SOF/VEL) with reduced in-person visits and laboratory monitoring. This analysis evaluated the association of adherence with sustained virologic response (SVR) and correlates of adherence.
**Methods:** 399 HCV treatment-naïve participants without decompensated cirrhosis were enrolled from Brazil, South Africa, Thailand, Uganda and US, and received 84 tablets of SOV/VEL at entry, with first dose observed. Adherence at week 4 (Wk 4) was self-reported remotely and grouped as ALL vs.<ALL. At Week 24 time to complete SOV/VEL was self-reported and grouped as TIMELY (completed treatment in 84 ± 7 days) vs. NOT TIMELY. GOOD adherence was defined as ALL at Week 4 and TIMELY at Week 24. Correlates of <GOOD adherence were explored using logistic regression.

**Results:** Ninety-five percent (379/399) of participants achieved SVR. At Wk 4, 93% (368/395) reported taking ALL SOFV/VEL doses; only 27 participants (7% of total) reported<ALL vs. 96% (355/368) of those who reported ALL at Week 4 achieved SVR (p< 0.01). Ninety-two percent (362/395) reported TIMELY adherence and 88% (346/392) GOOD adherence. Adherence at Week 24 and the composite adherence measure, GOOD, were not associated with SVR. Age <30, current or previous substance use, current psychiatric medication use, and US site were associated with <GOOD adherence. In multivariate regression, all but psychiatric medication use remained significant (Table 1).

**Conclusion:** Overall, self-reported adherence in this trial was high. Self-reported adherence during the first 4 weeks of SOF/VEL was associated with achieving SVR. Programs seeking to scale up the minimal monitoring strategy may consider additional support for younger individuals or those reporting current or past substance use. Week 4 self-reported adherence may also help identifying those who may need additional support.

**Table 1: Baseline Correlates of <GOOD Adherence among participants in the A5360 (MINMON) trial.**

| Participant Characteristics | # Participants | Univariable Logistic Regression Models Odds Ratio | | Main Effects Logistic Regression Model Odds Ratio | |
|---|---|---|---|---|---|
| | | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Age <30 years (vs ≥30) | 33 vs 366 | 3.86 (1.75-8.52) | <0.01 | 4.38 (1.83-10.50) | <0.01 |
| Female sex at birth (vs Male) | 139 vs 260 | 0.78 (0.42-1.47) | 0.45 | | |
| HCV Diagnosis >1yr prior (vs ≤ 1yr) | 289 vs 110 | 0.96 (0.50-1.82) | 0.90 | | |
| Substance† use (vs not) | 56 vs 343 | 2.60 (1.30-5.18) | <0.01 | 2.23 (1.07-4.63) | 0.03 |
| Daily Alcohol use (vs not) | 11 vs 388 | 0.65 (0.08-5.15) | 0.68 | | |
| Current Psychiatric meds (vs not) | 61 vs 338 | 2.57 (1.31-5.05) | <0.01 | | |
| Living with HIV (vs not) | 166 vs 233 | 0.83 (0.46-1.51) | 0.54 | | |
| Polypharmacy‡ (vs not) | 56 vs 343 | 1.52 (0.71-3.23) | 0.28 | | |
| Region: Africa vs US | 27 vs 131 | 0.54 (0.17-1.67) | <0.01 | 0.49 (0.15-1.60) | <0.01 |
| Region: Asia vs US | 110 vs 131 | 0.18 (0.07-0.45) | | 0.17 (0.07-0.44) | |
| Region: South America vs US | 131 vs 131 | 0.28 (0.14-0.59) | | 0.33 (0.16-0.70) | |

†Substance use was defined as: current or previous usage of any of the following within 3 months prior to trial entry: amphetamines, hallucinogens, cocaine, opioids, or sedatives (not Alcohol or Cannabis).
‡Polypharmacy was defined as: more than 5 other medications, not including antiretrovirals.

## 531 IMPACT OF SVR WITH DAAs IN COINFECTED PATIENTS WITH ADVANCED FIBROSIS/CIRRHOSIS

**Teresa Aldámiz-Echevarría**[1], Juan Berenguer[1], Victor Hontañón[2], Chiara Fanciulli[1], Carmen Quereda[3], Carmen Busca Arenzana[2], Lourdes Domínguez[4], Cristina Hernandez Gutierrez[5], Jorge Vergas[6], Gabriel Gaspar[7], Lucio Jesús García-Fraile Fraile[8], Marta De Miguel[9], José M. Bellón[1], Juan González-García[2]
*[1]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]La Paz University Hospital, Madrid, Spain, [3]Hospital Universitario Ramón y Cajal, Madrid, Spain, [4]Hospital Universitario 12 de Octubre, Madrid, Spain, [5]Hospital Universitario Príncipe de Asturias, Madrid, Spain, [6]Hospital Universitario Clínico San Carlos, Madrid, Spain, [7]Hospital Universitario de Getafe, Madrid, Spain, [8]Hospital Universitario de La Princesa, Madrid, Spain, [9]Fundación SEIMC-GeSIDA, Madrid, Spain*

**Background:** Direct-acting antivirals (DAAs) are highly successful in HIV/HCV-coinfected patients with advanced fibrosis (F3) or cirrhosis (F4), but little is known about their impact on clinical events.

**Methods:** We studied coinfected patients with F3/F4 with a sustained viral response (SVR) following all-oral DAA-Rx (Rx) from 2014 to 2017 in observational GeSIDA cohorts (Spain). The censoring date was December 31, 2019. The primary outcome was time from the finalization of DAA-Rx to clinical progression (CP), defined as decompensation (DEC), hepatocellular carcinoma (HCC), or death, whichever occurred first. Variables included liver disease category (F3, compensated F4 [F4c], and decompensated F4 [F4d]), age, sex, current smoking, current high alcohol intake (>50 g/d), prior AIDS-defining conditions, metabolic syndrome (AHA/NHLBI criteria), CD4+ cell count, serum albumin, liver stiffness (LS), FIB4 index, triglyceride and glucose index (TyG), hepatic steatosis index (HIS); and % decrease in LS (D-LS) and % decrease in FIB4 (D-FIB4) 1 year after finalization of DAA-Rx. Multivariable Cox regression analysis, with multiple imputations by chained equations for missing data, was used to assess the effect of the independent variables on the outcome.

**Results:** A total of 1300 patients were included with a median age of 52 years; 79% males; 87% prior injection drug use; 98% on ART; 94% with undetectable HIV-RNA; median CD4+ 525 cells/mm$_3$. Liver disease: 384 (30%) F3, 761 (59%) F4c, and 155 (12%) F4d. After a median follow-up of 40.9 (34.5 – 45.1) months, 89 patients were lost, 85 died, 65 had a new LRE (DEC or HCC), and 30 were diagnosed with HCC. The frequency and indicence rate of outcomes by liver disesase category is shown in the Table. The following variables were found to be independently associated with CP: F4d (vs F3) (adjusted hazard ratio [aHR] 2.25; 95%CI 1.09-4.65, P=.029), male sex (aHR 1.99; 95%CI 1.17-3.37, P=.011), age (aHR 1.06; 95%CI 1.03-1.10, P=.001), LS (aHR 1.03; 95%CI 1.01-1.04, P<.001), D-LS (aHR 0.98; 95%CI 0.98-0.99, P<.001), and serum albumin (aHR 0.59; 95%CI 0.44-0.79, P<.001).

**Conclusion:** Our results suggest that among coinfected patients with well-controlled HIV and with advanced F3/F4, the risk of CP following DAA-induced SVR increased with liver disease severity at the beginning of therapy and with a lower decrease in LS one year after its finalization. Further work should be done to develop prediction scores to inform clinical decision-making in this population group.

**Table.** Frequency and indicence rate (IR) x 100 person-years of outcomes according to the different liver disesase categories†

| | Person-time | Events | IR (95% CI) |
|---|---|---|---|
| **Clinical Progression** | | | |
| All patients | 3992.5 | 129 | 3.231 (2.719 - 3.840) |
| Advanced fibrosis (F3) | 1185.3 | 16 | 1.350 (0.827 - 2.203) |
| Compensated cirrhosis (F4c) | 2378.0 | 72 | 3.028 (2.403 - 3.814) |
| Decompensated cirrhosis (F4d) | 429.1 | 41 | 9.554 (7.035 - 12.975) |
| **Death** | | | |
| All patients | 4120,7 | 85 | 2.063 (1.668 - 2.551) |
| Advanced fibrosis (F3) | 1190.3 | 13 | 1.092 (0.634 - 1.881) |
| Compensated cirrhosis (F4c) | 2438,5 | 47 | 1.927 (1.448 - 2.565) |
| Decompensated cirrhosis (F4d) | 429.0 | 25 | 5.082 (3.434 - 7.521) |
| **Liver-related event‡** | | | |
| All patients | 3992.5 | 65 | 1.628 (1.277 - 2.076) |
| Advanced fibrosis (F3) | 1185.3 | 4 | 0.337 (0.127 - 0.899) |
| Compensated cirrhosis (F4c) | 2378.0 | 37 | 1.556 (1.127 - 2.147) |
| Decompensated cirrhosis (F4d) | 429.1 | 24 | 5.592 (3.748 - 8.344) |
| **Hepatocellular carcinoma** | | | |
| All patients | 3966.7 | 30 | 0.756 (0.529 - 1.082) |
| Advanced fibrosis (F3) | 1171.0 | 4 | 0.342 (0.128 - 0.910) |
| Compensated cirrhosis (F4c) | 2328.1 | 17 | 0.730 (0.454 - 1.175) |
| Decompensated cirrhosis (F4d) | 467.7 | 9 | 1.924 (1.001 - 3.698) |

†Defined by TE, liver biopsy, and clinical-biological parameters. The TE cut-offs were > 9.9 and ≤ 12.5 kPa for F3, and > 12.5 kPa for F4. ‡ Decompensation (ascites, variceal bleeding, portosystemic encephalopathy) or Hepatocellular carcinoma.

## 532 HIGHER MORTALITY OF PLWH CURED OF HCV BY DAAs: RESULTS FROM THE ANRS-CO4-FHDH COHORT

New Investigator Scholar

**Maria B. Requena**[1], Sophie Grabar[2], Gilles Pialoux[3], Dominique Costagliola[1], Karine Lacombe[4]
*[1]Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France, [2]AP-HP, Unité de Santé Publique, Hôpital Saint-Antoine, Paris, France, [3]AP-HP, Service des Maladies Infectieuses et Tropicales, Hôpital Tenon, Hôpitaux Universitaires de l'Est Parisien, Paris, France, [4]AP-HP, Service des Maladies Infectieuses et Tropicales, Hôpital Saint-Antoine, Paris, France*

**Background:** Hepatitis coinfection increases mortality in people who live with HIV (PLWH). New direct-acting antivirals (DAAs) lead to a 95% cure rate and decreased complications in monoinfected patients with Hepatitis C virus (HCV). This study aimed to compare all-cause mortality in virally suppressed PLWH (<200 copies/mL) cured of HCV by DAAs to all-cause mortality in virally suppressed HIV monoinfected individuals of the nationwide ANRS-CO4 French Hospital Database on HIV (FHDH) cohort.

**Methods:** The study included cured HCV PLWH with controlled HIV viral load who started DAAs between September 2013 and September 2018. They were matched on age (+/-5 years), gender, HIV transmission route (men who have sex with men -MSM- intravenous drug user -IVDU- or other), AIDS status, and BMI (+/-1) to up to 10 HIV monoinfected patients with controlled HIV viral load followed at the index date (date of HCV cure). Poisson regression with robust variance estimates were used to compare mortality in both groups accounting for age, gender, HIV transmission route, AIDS status, year of first HIV diagnosis, CD4 nadir, and BMI.

**Results:** 3,574 PLWH cured of HCV by DAAs (G1) and 28,846 monoinfected PLWH (G2) were included. Median follow-up (FU) time was 2.2 years in G1 (interquartile range (IQR): 1.3-2.9), and 2.0 years (IQR: 1.1-2.7) in G2. Median age was 52.1 years (IQR: 47.3-56.0) and 24,734 (76.3%) were men. In G1, 311 (8.7%) had cirrhosis. One hundred and ten deaths occurred in G1 and 384 in G2. The absolute risk of death in G1 remained constant between 0-18 months and 18-36 months (incidence rate (IR) /1000 PY: 13.5 [10.4; 17.1] vs. 14.7 [10.5; 20.0]), while the absolute risk of death in G2 was lower after the first 18 months (IR /1000 PY: 8.2 [7.3; 9.1] vs. 4.8 [3.8; 5.9]). G1 was associated with a higher risk of all-cause death, incidence rate ratio IRR: 1.59 [0.97-2.62]. The IRR of death in G1 relative to G2 was higher after 18 months of FU, IRR 0-18 months: 1.34 [0.76-2.38], IRR 18-36 months: 2.42 [1.40-4.20].

**Conclusion:** Despite HCV cure and HIV viral suppression, HCV-coinfected PLWH cured by DAAs are, for now, at higher risk of all-cause mortality than monoinfected PLWH, even after controlling for CD4 nadir. The absolute risk of death in HIV monoinfected participants is much lower in the 18-36 month period compared to the 0–18-months period while it remains constant in HIV/HCV co-infected participants cured by DAAs.

## 533 DIAGNOSIS OF ESOPHAGEAL VARICES IN VIRUS-RELATED ADVANCED CHRONIC LIVER DISEASE

**Jordana Serero[1],** Amine Zoughlami[1], Stephen E. Congly[2], Irene Zhao[2], Julie Zhu[3], Alnoor Ramji[4], Curtis Cooper[5], Philip Wong, Robert Bailey[7], Carla S. Coffin[2], Giada Sebastiani[6]

*[1]McGill University, Montreal, Canada, [2]University of Calgary, Calgary, Canada, [3]Dalhousie University, Halifax, Canada, [4]British Columbia Centre for Disease Control, Vancouver, Canada, [5]Ottawa General Research Institute, Ottawa, Canada, [6]McGill University Health Centre, Montreal, Canada, [7]Alberta Health Services, Calgary, Canada*

**Background:** Hepatitis C (HCV) and hepatitis B (HBV) viruses represent a major cause of compensated advanced chronic liver disease (cACLD). People with HIV are also at high risk for cACLD due to fatty liver. The development of portal hypertension and esophageal varices (EV) impacts on prognosis of cACLD. Esophagogastroduodenoscopy (EGD) is the gold standard to diagnose EV in cACLD. Baveno VI and expanded Baveno VI criteria, based on combining liver stiffness measurement (LSM) with platelets, have been proposed to avoid unnecessary EGD for large esophageal varices needing treatment (EVNT). Simple fibrosis biomarkers have also been proposed for non-invasive diagnosis of EVNT. We aimed to validate and compare LSM based criteria and simple fibrosis biomarkers to diagnose EVNT in virus-related cACLD.

**Methods:** The Canadian Hepatitis B Network and LIVEHIV cohorts were utilized to perform a cross-sectional analysis of patients who underwent LSM in 2014-2020. Inclusion criteria were: a) diagnosis of cACLD, defined as LSM>10 kPa; b) availability of EGD and platelets within 1 year of LSM. Baveno VI (LSM150,000) and extended Baveno VI criteria (LSM110,000) were tested for EGD sparing. Diagnostic performance of these criteria against EGD was computed and compared to the simple fibrosis biomarkers fibrosis-4 index (FIB-4), AST-to-Platelets Ratio Index (APRI) and AST-to-ALT ratio (AAR). Optimized cut-offs of these biomarkers to diagnose EVNT were established by using the area under the curve analysis.

**Results:** A total of 340 patients (mean age 55, 33% female, 30.6% with HIV, 25.3% with HBV and 44.1% with HCV) were included. The prevalence of any grade EV and EVNT was 32.8% and 8.8% in the whole cohort, 31.3% and 2.6% in HIV patients, 30.2% and 9.3% in HBV and 35% and 13% in HCV, respectively. Table 1 reports the diagnostic performance of the non-invasive criteria across the etiology of cACLD. Both Baveno VI and expanded Baveno VI criteria performed well in patients with virus-related cACLD. The optimized cut-offs for fibrosis biomarkers were: FIB-4 3.3, APRI 1.5, AAR 1.0. There was no difference on performance of the fibrosis biomarkers compared to LSM-based criteria.

**Conclusion:** These results support the use of non-invasive criteria based on LSM and platelets to spare unnecessary EGD in virus-related cACLD. Simple fibrosis biomarkers can also ameliorate resource utilization and avoid invasive testing in context of screening EGD for patients with virus-related cACLD.

**TABLE 1:** Performance of non-invasive criteria for prediction of EVNT.

| | Sensitivity (%) | Specificity (%) | NPV (%) | PPV (%) | Spared EGD (%) | EVNT missed (%) |
|---|---|---|---|---|---|---|
| **HIV** (n=104) | | | | | | |
| Baveno VI | 80 | 22 | 92.8 | 8 | 20.4 | 1.6 |
| Extended Baveno VI | 80 | 40.7 | 96 | 10.2 | 31.2 | 1.6 |
| FIB-4 | 100 | 68.9 | 100 | 8 | 60.5 | 0 |
| APRI | 50.0 | 56.7 | 98.1 | 2.5 | 68.4 | 1.3 |
| AAR | 50.0 | 47.3 | 97.2 | 2.5 | 47.4 | 1.3 |
| **HBV** (n=86) | | | | | | |
| Baveno VI | 100 | 32.1 | 100 | 13.1 | 29.1 | 0 |
| Extended Baveno VI | 75.0 | 56.4 | 96.6 | 15.0 | 51.1 | 2.3 |
| FIB-4 | 75.0 | 72.0 | 96.4 | 22.2 | 67.5 | 2.4 |
| APRI | 62.5 | 84 | 95.5 | 29.4 | 79.5 | 3.6 |

## 534 HIV/HBV/HCV TRIPLE INFECTION, END-STAGE LIVER DISEASE, AND ALL-CAUSE MORTALITY

**Amanda Mocroft[1],** Adam Geressu[2], Charles Béguelin[3], Josep María Llibre[4], Jeffrey V. Lazarus[5], Janez Tomazic[6], Jelena Smidt[7], Milosz Parczewski[8], Johanna Brännström[9], Dalibor Sedlacek[10], Olaf Degen[11], Marc van der Valk[12], Dzmitry Paduta[13], Lars Peters[14]

*[1]Rigshospitalet, Copenhagen, Demark, [2]Royal Liverpool University Hospital, Liverpool, UK, [3]University Hospital of Bern, Bern, Switzerland, [4]Hospital Germans Trias i Pujol, Barcelona, Spain, [5]Barcelona Institute for Global Health, Barcelona, Spain, [6]Department of Infectious Diseases, Ljubljana University Medical Center, Ljubljana, Slovenia, [7]Narva AIDS Centre, Kohtla-Järve, Estonia, [8]Pomeranian Medical University, Szczecin, Poland, [9]Department of Infectious Diseases, Venhälsan, Södersjukhuset, Sweden, [10]Charles University Hospital Plzen, Plzen, Czech Republic, [11]University Hospital Hamburg–Eppendorf, Hamburg, Germany, [12]Stichting HIV Monitoring, Amsterdam, Netherlands, [13]Gomel Regional Centre for Hygiene, Gomel, Belarus, [14]Rigshospitalet, Copenhagen, Denmark*

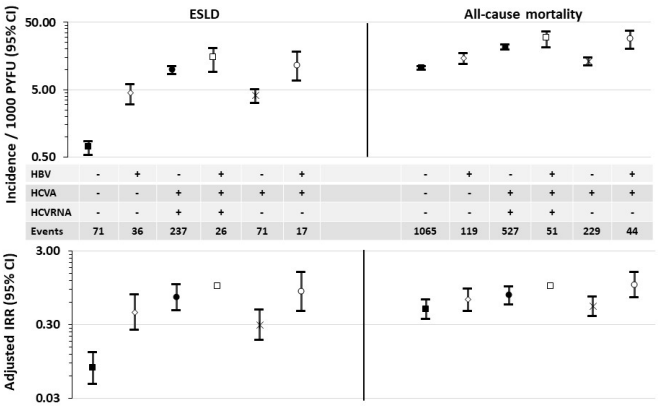
**Background:** It is well known that persons living with HIV (PLHIV) coinfected with either hepatitis B (HBV) or hepatitis C virus (HCV) have increased rates of end stage liver disease (ESLD) and all-cause mortality, but less is known about HIV/HBV/HCV triple infection compared to PLHIV with HBV or HCV dual infections.

**Methods:** All PLHIV under follow-up in EuroSIDA aged >18 at baseline were followed to end-stage liver disease (ESLD), death, last visit, or 31/12/2019. Baseline was defined as the first date with known HBV, HCVA and HCVRNA status after the later of 1/1/2001 or EuroSIDA enrolment. PLHIV ESLD was defined as ascites, hepatorenal syndrome, grade III/IV hepatic encephalopathy, liver decompensation, oesophageal variceal bleeding, spontaneous bacterial peritonitis, liver transplantation, hepatocellular carcinoma, unspecified ESLD or death from liver disease. Poisson regression compared 6 groups updated over time; HIV; HIV/HBV, HIV/HCVA/HCVRNA+, HIV/HCVA/HCVRNA-, HIV/HBV/HCVA/HCVRNA+, HIV/HBV/HCVA/HCVRNA-.

**Results:** Among 16,584 included PLHIV, at baseline 298 (1.8%) were HIV/HBV/HCVA/HCVRNA+ and 4108 (24.8%) were HIV/HCVA/HCVRNA+. In total, 458 PLHIV developed an ESLD event during 153,899 PYFU (incidence rate [IR] 3.0/1000 PYFU; 95% CI 2.7–3.3) and 2035 died during 154,913 PYFU (13.1; 12.6–13.7). Crude ESLD rates (Figure) were higher in HIV/HBV/HCVA/HCVRNA+ vs. HIV/HCVA/HCVRNA+, 15.0 (9.2-20.7) vs. 9.8 (8.6-11.1), respectively. HIV/HBV/HCVA/HCVRNA+ had the highest proportion of deaths due to liver disease, which remained unchanged over time. For all-cause mortality the rates were 29.0 (21.0-37.0) vs. 21.5 (19.7-23.3). After adjustment (figure), compared to those with HIV/HBV/HCVA/HCVRNA+, PLHIV with HIV/HCVA/HCVRNA+ had statistically significantly lower rates of all-cause mortality (aIRR 0.75; 95% CI 0.56–1.00) and similarly reduced but non-significant rates of ESLD (0.71; 0.47-1.06). These differences remained unchanged through study calendar years (p=0.14, interaction).

**Conclusion:** HIV/HBV/HCVA/HCVRNA+ PLHIV had higher rates of ESLD and all-cause mortality than those with HIV/HCVA/HCVRNA+. After adjustment, the increased rate of ESLD in HIV/HBV/HCVA/HCVRNA+ vs. HIV/HCVA/HCVRNA+ was not statistically significant, possibly due to limited power, but the higher rates for all-cause mortality remained. Strategies aimed at ensuring HBV and HCV treatment still need to be prioritized in PLHIV with triple infection in Europe.

ESLD and all-cause mortality stratified by latest HBV and HCVA/HCVRNA status




*adjusted for gender, HIV transmission category, region of Europe, nadir CD4, age, liver fibrosis stage, and prior ESLD (baseline); smoking, diabetes, CD4 count, HIV viral load, calendar year of follow-up and proportion of follow-up time treated with TDF/TAF±XTC as time-updated variables. All-cause mortality adjusted additionally for ethnicity, prior clinical diagnoses (AIDS, CVD, extrahepatic NADM), and BMI, all fixed at baseline

## 535 IMPACT OF HCV CURE ON DEPRESSIVE SYMPTOMS IN THE HIV-HCV COINFECTED POPULATION

New Investigator Scholar

**Gayatri J. Marathe**[1], Erica E. Moodie[1], Marie-Josée Brouillette[1], Charlotte Lanièce Delaunay[1], Joseph Cox[1], Curtis Cooper[2], M. John Gill[3], Valérie Martel-Laferrière[4], Neora Pick[5], Marie-Louise Vachon[6], Sharon Walmsley[7], Marina B.

Klein[8]
*[1]McGill University, Montreal, Canada, [2]University of Ottawa, Ottawa, Canada, [3]University of Calgary, Calgary, Canada, [4]Centre Hospitalier de l'Université de Montréal, Montreal, Canada, [5]Oak Tree Clinic, BC Women's Hospital, Vancouver, Canada, [6]Centre Hospitalier Universitaire de Québec-Université Laval, Quebec, Canada, [7]University of Toronto, Toronto, Canada, [8]McGill University Health Centre, Montreal, Canada*

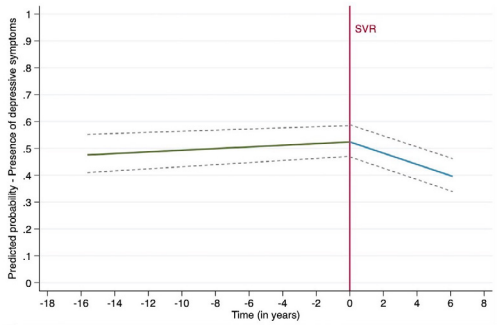
**Background:** Depression is common in the HIV-HCV co-infected population due to direct neurocognitive effects of HCV and/or stigma, discrimination and socioeconomic burdens associated with HCV, HIV, and drug use. Direct acting antivirals (DAAs) result in high rates of HCV cure with minimal side-effects. We assessed the impact of sustained virologic response (SVR) after HCV treatment on depressive symptoms, in the era of second generation DAAs (between 2013-2020), in the HIV-HCV co-infected population in Canada.

**Methods:** We used data from the Canadian Co-infection Cohort, a multicentre prospective cohort, and its associated sub-study on food insecurity. We predicted Center for Epidemiologic Studies Depression Scale-10 classes for depressive symptoms indicative of a depression risk (outcome) using a random forest classifier and corrected for misclassification. We included participants who achieved SVR (exposure) and fitted a segmented modified Poisson model using an interrupted time series design. We included time from cohort entry to DAA initiation in the pre-exposure period and time after SVR in the post-exposure period. The model was adjusted for time-varying confounders - advanced fibrosis/cirrhosis (AST to Platelet Ratio Index (APRI)≥1.5), detectable HIV viral load (>50 copies/ml), low CD4 cell count (≤250 cells/µl), current injection drug use, current alcohol use, incarceration in the past 6 months and antidepressant use.

**Results:** We included 511 participants; predominantly male (70%) with a baseline median age of 47 years (IQR: 41-52) and 56% prevalence of depressive symptoms. Most had no post-secondary education (71%) and were unemployed (69%) at baseline. Median follow-up was pre-SVR: 3 years (IQR: 1.4-5.5) and post-SVR: 1.8 years (IQR: 1.1-2.4). The model showed stable pre-SVR trends for depressive symptoms and no immediate level change on achieving SVR. However, the post-SVR trends suggested a decrease over time in presence of depressive symptoms, decreasing 5% per year (adjusted risk ratio: 0.95 (95%CI: 0.94-0.96)); see figure 1.

**Conclusion:** Depressive symptoms showed steady decline over time among patients cured from HCV in the DAA era. Improvements in depression after cure may reflect changes in biological pathways leading to depression related to HCV, improved general health and possibly lower HCV related stigma, and discrimination. The durability and mechanisms for reduced depression should be elucidated in future studies with extended follow-up.

**Figure 1:** Depressive symptom trends pre- and post-SVR in the second-generation DAA era (2013-2020) with model estimates




| N | Risk ratios (95% CI) * | | |
|---|---|---|---|
| | Pre-SVR trends per year | Level change at SVR | Post-SVR trends per year |
| 511 | 1.01 (1.01-1.02) | 1.00 (0.97-1.03) | 0.95 (0.94-0.96) |

Abbreviations: SVR: Sustained virologic response; DAA: Direct acting antivirals; CI: Confidence intervals

## 536 HCV DIAGNOSIS PRECEDING AN HIV OUTBREAK AMONG PWID IN KANAWHA COUNTY, WV, 2019–2021

**Alana G. Hudson**[1], Robert A. Bonacci[2], Anne C. Moorman[2], McKenna Penley[2], Suzanne Wilson[1], Robert P. McClung[2], Jessica Hoffman[1], Erica Thomasson[2], Danae Bixler[2]
*[1]West Virginia Department of Health and Human Resources, Charleston, WV, USA, [2]Centers for Disease Control and Prevention, Atlanta, GA, USA*

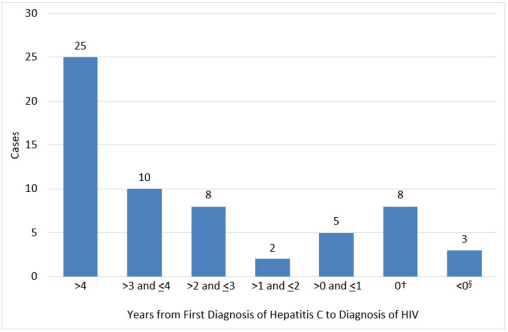
**Background:** Recent HIV outbreaks among people who inject drugs (PWID) have featured high rates of hepatitis C (HCV) co-infection, and incidence of acute hepatitis C has been used to identify United States counties vulnerable to future HIV/HCV outbreaks. Historically, in West Virginia (WV), incidence of acute hepatitis A virus (HAV), hepatitis B virus (HBV) and HCV infection among PWID has been high, but HIV incidence has been low in most areas of the state. In 2019, the WV Department of Health and Human Resources Bureau for Public Health detected an increase in HIV diagnoses among PWID in Kanawha County, an area disproportionately affected by the opioid crisis. We describe the frequency and timing of viral hepatitis diagnosis relative to HIV diagnosis in this outbreak.

**Methods:** For PWID residing in Kanawha County, WV, with HIV diagnosed during 1/1/2019–6/18/2021, we analyzed HIV and viral hepatitis data from the WV HIV surveillance system, WV viral hepatitis and immunization registries, and from medical records at a large integrated health care system and a community clinic. We performed descriptive analyses including frequencies and measures of central tendency.

**Results:** Among 65 PWID with HIV, 61 (94%) were seropositive for HCV infection. HCV diagnosis preceded HIV diagnosis for 50 individuals (82%), with a median interval of 46 months (interquartile range [IQR], 29–71) (figure); HCV diagnosis occurred concurrently or after HIV diagnosis for 8 (13%) and 3 (5%) individuals, respectively. History of HAV infection (11, 17%) or HBV infection (10, 15%) were less common. The median times from HAV or HBV diagnosis to HIV diagnosis were 22 (IQR, 15–31) and 30 (IQR, 2–67) months, respectively. Overall, only 32% and 34% of individuals had evidence of receiving at least one hepatitis A (HepA) or hepatitis B (HepB) vaccine dose, respectively.

**Conclusion:** As in prior recent HIV outbreaks among PWID, we found co-infection with HCV was high. In this outbreak, HCV diagnosis often preceded HIV diagnosis by multiple years, indicating that HCV diagnosis is an important indicator of risk for HIV acquisition. Our findings underscore the importance of integrated HIV/HCV testing and prioritizing proactive expansion of prevention and treatment services, including syringe services, medication for opioid use disorder, HIV pre-exposure prophylaxis, and HepA/HepB vaccines, to counties with high HCV incidence. HCV diagnosis represents a key opportunity to enhance linkage to those prevention and treatment services for PWID.

Figure. Years from First Diagnosis of Hepatitis C to Diagnosis of HIV Among Persons who Inject Drugs in an HIV Outbreak — Kanawha County, WV, 2019–2021; N=61*




*Four cases had negative HCV laboratory studies
†Eight cases of HIV and HCV infection were diagnosed within one week of each other
§The <0 category represents persons for whom HCV infection was diagnosed after HIV infection

## 537 THE HEPATITIS C CARE CONTINUUM IN THE DAA ERA AMONG TRANSGENDER WOMEN WITH HIV

**Jimmy Ma**[1], Stephanie A. Ruderman[1], Bridget M. Whitney[1], Rob J. Fredericksen[1], John D. Scott[1], Robin M. Nance[1], Sari L. Reisner[2], Kenneth H. Mayer[3], Jamaica R. Robinson[4], Joseph A. Delaney[5], Edward R. Cachay[6], Geetanjali Chander[7], H Nina Kim[1], Lydia N. Drumright[1]
*[1]University of Washington, Seattle, WA, USA, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]The Fenway Institute, Boston, MA, USA, [4]Columbia University, New York, NY, USA, [5]University of Manitoba, Winnipeg, Canada, [6]University of California San Diego, La Jolla, CA, USA, [7]The Johns Hopkins University, Baltimore, MD, USA*

**Background:** Recent studies of transgender women (TW) with HIV found greater hepatitis C (HCV) prevalence and decreased retention in HIV care compared to cisgender men and women (CM, CW). HIV risk factors in TW are relatively well described, but little is known about risk factors for HCV infection and outcomes in TW with HIV, which are crucial gaps for HCV elimination. We describe one of the first studies on the HCV care continuum in TW with HIV in

the direct-acting antiviral (DAA) era.

**Methods:** We conducted a cross-sectional study of all adult TW with HIV in the CFAR Network of Integrated Clinical Systems cohort (1/2014-3/2021). We matched TW 1:4 with CM and CW on age, site, and last visit date. Care continuum outcomes were based on most recent data and included HCV infection, active viremia, DAA receipt, and sustained virologic response (SVR) (HCV RNA <25 IU/mL or undetectable ≥10 weeks after end of DAA for variability in testing). We used race/ethnicity-adjusted logistic regression models (aOR) to assess differences in these outcomes by gender. We also considered other clinical risk factors including injection drug use (IDU) for the HCV infection outcome.

**Results:** Of 297 TW with HIV in care since 2014, 59 had current/prior HCV infection, 43 (73% of HCV infected) were viremic, 15 (35% of viremic) received DAAs, and 9 of 10 with post-DAA labs had SVR. Compared to CM and CW, TW were more likely to identify as non-white (82% vs 57% CM, 74% CW, p<0.01) but were similar with respect to HIV suppression, FIB-4 ≥3.25, missed visits in last year, and IDU (HIV risk factor). Compared to CM, TW were more likely to have HCV infection (aOR 1.70, p<0.01) and active HCV viremia (aOR 1.54, p=0.03). Compared to CW, TW had similar outcomes in all race/ethnicity-adjusted analyses but were more likely to have HCV infection after adjusting for both IDU and race/ethnicity (OR 1.68, p=0.01).

**Conclusion:** TW with HIV were more likely HCV infected compared to CM and CW, especially after adjusting for IDU, and viremic compared to CM. However, once in care, TW accessed DAAs as readily as cisgender persons with HIV (PWH). Given higher HCV risk and low DAA initiation, TW with HIV in particular may benefit from close HCV screening, tailored prevention efforts especially for IDU, and scale up of DAA treatment. While overall DAA initiation rates are low, rates are higher in more recent years. However, a significant need still exists to prioritize DAAs for all PWH with HCV to improve elimination in a highly vulnerable population.

**Table. Matched analysis of HCV care continuum outcomes in the DAA era among transgender women with HIV compared to cisgender individuals with HIV in CNICS.**

| HCV Care Continuum Outcome[a] | TW (N=297) | CM (N=1186) | CW (N=1112) | Transgender women vs Cisgender men | | | Transgender women vs Cisgender women | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | OR[b] | 95% CI | P | OR[b] | 95% CI | P |
| HCV infection[c] | 59 | 152 | 127 | 1.64 | 1.18, 2.29 | <0.01 | 1.30 | 0.92, 1.83 | 0.1 |
| Adjusted for Race/Ethnicity | - | - | - | 1.70 | 1.21, 2.38 | <0.01 | 1.44 | 0.996, 2.08 | 0.053 |
| Adjusted for IDU (HIV Risk Factor)[d] | - | - | - | 1.61 | 1.10, 2.36 | 0.01 | 1.68 | 1.13, 2.50 | 0.01 |
| Active HCV Viremia[e] | 43 (73% of infection) | 120 (79% of infection) | 102 (80% of infection) | 1.45 | 0.998, 2.10 | 0.051 | 1.20 | 0.81, 1.77 | 0.4 |
| Adjusted for Race/Ethnicity | - | - | - | 1.54 | 1.05, 2.25 | 0.03 | 1.30 | 0.86, 1.97 | 0.2 |
| Receipt of DAA | 15 (35% of viremic) | 54 (45% of viremic) | 40 (39% of viremic) | 1.10 | 0.60, 2.00 | 0.8 | 1.06 | 0.58, 1.97 | 0.8 |
| Adjusted for Race/Ethnicity | - | - | - | 1.20 | 0.67, 2.18 | 0.5 | 1.19 | 0.59, 2.40 | 0.6 |

Transgender women are matched 1:4 with cisgender individuals on age (within 5 years), CNICS site, and last clinic visit date (within 6 months).

Abbreviations: CI, confidence interval; CM, cisgender men; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; CW, cisgender women; DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; OR, odds ratio; TW, transgender women.

[a]Outcomes and exposures based on the most recent lab or clinical visit. A total of 10 TW with HIV had post-DAA labs available for the sustained virologic response outcome; insufficient numbers to conduct additional analyses so not included here for clarity.
[b]Logistic regression models comparing transgender women to cisgender individuals (referent) for specific HCV care continuum outcomes. ORs represent bivariate analyses (non indented rows) and adjusted models (indented rows) of the bivariate model in the parent row immediately above.
[c]HCV infection defined as any positive HCV antibody, RNA, or genotype or receipt of DAA.
[d]Adjusting for IDU (HIV Risk Factor) in addition to race/ethnicity for HCV infection outcome. Other clinical factors analyzed for HCV infection not displayed due to lack of substantial change in estimates after adding to models adjusting for IDU (HIV risk factor) and race/ethnicity. Other clinical factors included nadir and current CD4, FIB-4 ≥3.25, log-transformed HIV RNA, and percent missed visits in last year.
[e]Active HCV viremia defined as any positive HCV RNA or genotype.

## 538 PROGRESS TOWARD HCV MICROELIMINATION AMONG HIV-POSITIVE PATIENTS IN TAIWAN

**Shu-Yuan Ho**[1], Li-Hsin Su[1], Hsin-Yun Sun[1], Miao-Hui Huang[2], Yu-Shan Huang[1], Sung-Hsi Huang[3], Yi-Chia Huang[3], Wen-Chun Liu[1], Yi-Ching Su[1], Sui-Yuan Chang[1], Chien-Ching Hung[1]

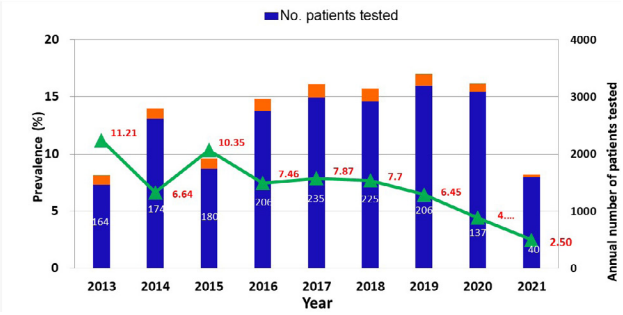
*[1]National Taiwan University Hospital, Taipei, Taiwan, [2]Tzu Chi Hospital, Hualien, Taiwan, [3]National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan*

**Background:** Taiwan has committed to achieving HCV elimination by 2025. HCV testing and antiviral treatments are reimbursed by the National Health Insurance. Interferon/ribavirin used to be the standard regimen of antiviral treatment and direct-acting antivirals (DAAs) were not reimbursed until 2017. Criteria for enrollment in HCV treatment program had been revised on an annual basis to lift the restrictions on access to HCV care and DAA treatment stepwise. Acute HCV infections were included in the treatment program in 2019. We aimed to examine the progress toward HCV microelimination among people living with HIV (PLWH) who had HCV viremia.

**Methods:** PLWH seeking care between 2013 and 2021 received HCV serological testing at least once annually. Those who tested HCV-seropositive at baseline or who received antiviral treatments with achievement of spontaneous clearance or sustained virological response (SVR) underwent HCV RNA testing at least once annually. Between 2019 and 2021, those with episodes of sexually transmitted infections, having achieved spontaneous clearance or (SVR), or elevated aminotransferases underwent HCV RNA testing every 12 weeks for 48 weeks. We estimated the annual incidence rate and prevalence of HCV viremia from 2013 to 2021.

**Results:** During the 8-year study period, 4075 PLWH were included. The incidence rate of HCV viremia had increased from 29.86 per 1000 person-years of follow-up (PYFU) in 2013 to 53.97 per 1000 PYFU in 2015, which sustained until 2018 (50.49 per 1000 PYFU), when the incidence rates started to decrease to 28.99 per 1000 PYFU in 2020. The prevalence of HCV viremia had declined from 11.21% of PLWH tested in 2013 to 7.46% in 2016 (interferon/ribavirin era), and further decline from 7.87% in 2018 to 2.50% in 2021 (DAA era). Overall a significant decrease by 78% of HCV viremia was achieved (figure) between 2013 and 2021.

**Conclusion:** With the introduction of reimbursed HCV testing anti-HCV treatments, particularly DAAs, significant declines of HCV viremia were observed among PLWH who underwent regular testing in Taiwan.




## 539 THE IMPACT OF COVID-19 ON HCV MICRO-ELIMINATION IN MSM IN GERMANY

**Patrick Ingiliz**[1], Thomas Lutz[2], Knud C. Schewe[3], Stefan Mauss[4], Stefan Christensen[5], Natasha Martin[6], Sonia Jain[6], Feng He[6], Michael Sabranski[3], Jukka Hartikainen[1], Markus Bickel[2], Jürgen K. Rockstroh[7], Christoph Boesecke[7]

*[1]Center for Infectiology, Berlin, Germany, [2]Infektiologikum, Frankfurt, Germany, [3]ICH Study Center, Hamburg, Germany, [4]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany, [5]Center for Interdisciplinary Medicine, Muenster, Germany, [6]University of California San Diego, La Jolla, CA, USA, [7]Bonn University Hospital, Bonn, Germany*

**Background:** Men who have sex with men (MSM) have been identified as one subgroup with continuous HCV transmission and as a target for HCV micro-elimination efforts. We assess newly acquired HCV among MSM in Germany since the introduction of directly-acting antiviral agents (DAAs).

**Methods:** The German NoCo cohort consists of patients from six German HIV and hepatitis treatment sites providing care for more than 8000 HIV-positive MSM, and serving as primary care providers and HIV pre-exposure prophylaxis (PrEP) sites. Patients who were diagnosed with recently acquired HCV infection since 2014 were enrolled and are followed-up. Virologic data, HIV and HCV treatment data, risk factors and behavior as well as liver disease assessment is acquired regularly.

**Results:** Between January 2014, and October 2021, 237 MSM with recently acquired HCV infection were included. A majority were Caucasian (95%), and mean age was 45.3 years (standard deviation, SD, 9.57). At HCV diagnosis, median ALT level was 224 U/L (interquartile range, IQR, 86 – 521), and median HCV viral load was 475,000 IU/mL (IQR 66,955 – 3,005,882). The most prevalent HCV genotype were 1a (58.7%), and 4d (16%). The risk factors for HCV acquisition were as follows: MSM: 92.4%, intravenous drug use: 2.95%, intranasal drug use: 0.8%, other: 0.4%, unknown: 7.2%. A subgroup of 21 (8.9%) MSM were not co-infected with HIV, of whom 15 (71.4%) were using PrEP. Anti-HCV treatment with DAAs was documented in 165 patients (71.7%), 18 (7.8%) had a spontaneous clearance, and in 47 patients (20.4%) treatment was not started. DAAs were initiated a median 6.6 months (IQR 4 to 9.3) after diagnosis; all treated patients achieved a sustained virologic response (SVR), or treatment was still ongoing (16%). Between 2014-2019 27-36 patients were diagnosed with recently acquired HCV annually. In relation to all HIV-positive MSM under care, the incidence was 0.33 – 0.39% per year with no significant change over time. In 2020, a decline in HCV incidence to 0.28% was observed. In 2021 HCV incidence dropped to 0.02%. In the same period, the number of patients seen in the centers remained stable, and routine HCV testing returned to pre-pandemic levels by the end of 2020.

**Conclusion:** The German NoCo cohort demonstrated stable HCV incidence rates despite a broad use of DAAs. In 2021, however, micro-elimination goals were met, possibly due to behaviour changes related to the SARS-CoV-2 pandemic and associated containment measures.

**540 WITHDRAWN**

**541 PERFORMANCE OF HCV ANTIGEN ASSAY IN THE DIAGNOSIS OF ACUTE HCV INFECTION AMONG PLWH**

**Hsin-Yun Sun**[1], Li-Hsin Su[1], Yi Ting Chen[1], Wen-Chun Liu[1], Yi-Ching Su[1], Yu-Chung Chuang[1], Yu-Shan Huang[1], Wan-Da Liu[1], Po-Liang Lu[2], Chien-Ching Hung[1], Ming-Lung Yu[2]
*[1]National Taiwan University Hospital, Taipei, Taiwan, [2]Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan*

**Background:** HCV serologic testing is limited in the timely diagnosis of acute HCV infection because of delayed seroconversion among immunocompromised hosts and persistent seropositivity in individuals with past HCV infection. HCV RNA testing is costly when performed on a regular basis to diagnose acute HCV infection among the at-risk populations. The performance of HCV core antigen (HCVcAg) assay in the diagnosis of HCV infection among people living with HIV (PLWH) and HIV-negative men who have sex with men (MSM) is rarely assessed in the Asia-Pacific region.
**Methods:** Participants who had sexually transmitted infections (STIs), achieved HCV clearance by antivirals or spontaneously, or had elevated aminotransferases during the follow-up were defined as high-risk populations for acute HCV infection. During June 2019 and February 2021, serum samples from high-risk PLWH and HIV-negative MSM with STIs or on pre-exposure prophylaxis for HIV were subject to 3-stage pooled-serum HCV RNA testing every 3 months until detection of HCV viremia or completion of 1-year follow-up. The samples from 827 at-risk participants and 730 low-risk PLWH at enrollment and all of the archived samples preceding the detection of HCV RNA testing after enrollment were tested for HCVcAg assay.
**Results:** During the study period, 1639 blood samples collected from 741 high-risk and 730 low-risk PLWH, and 86 HIV-negative participants were tested for both HCVcAg assay and HCV RNA by pooled-serum HCV RNA testing (Table). Of the 62 samples tested positive for HCV RNA, 54 (87.1%) were tested positive for HCVcAg assay. Of the 1577 samples tested negative for HCV RNA, 1568 (99.4%) were tested negative for HCVcAg assay. The HCV RNA loads of the 8 individual samples with detectable HCV RNA but negativity for HCVcAg assay were 305, 429, 880, 1435, 1745, 4560, 6600, and 7150 IU/mL, respectively (median HCV RNA, 3.2 $\log_{10}$ IU/mL, range 2.5-3.9). The median HCV RNA load of the remaining 54 specimens with concordant results between HCV RNA testing and HCVcAg assay was 6.5 (range 1.3-8.5) $\log_{10}$ IU/mL. The positive predictive value of HCVcAg assay was 85.7% and negative predictive value was 99.5%.
**Conclusion:** HCVcAg assay has a high specificity in the diagnosis of HCV viremic infection among PLWH and HIV-negative MSM at risk for acute HCV infection. However, its sensitivity is compromised in those with a low HCV RNA load.

**542 HCV MICROELIMINATION AMONG PEOPLE LIVING WITH HIV IN SAN DIEGO: ARE WE ON TRACK?**

Late Breaking

**Jaskaran S. Cheema**[1], William C. Mathews[2], Adriane Wynn[2], Laura Bamford[2], Francesca Torriani[1], Lucas Hill[2], Amutha Rajagopal[2], Jeffrey Yin[1], Edward R. Cachay[1], Natasha Martin[2]
*[1]University of California San Diego, San Diego, CA, USA, [2]University of California San Diego, La Jolla, CA, USA*

**Background:** In 2020, San Diego County launched the Eliminate Hepatitis C Initiative, with an aim to reduce HCV incidence by 80% by 2030 compared to a 2015 baseline. In 2018, an initiative to scale-up HCV treatment among PLWH occurred at the UCSD Owen Clinic, which cares for roughly 25% of all PLWH with HCV in San Diego. We use epidemic modeling to assess the potential impact of treatment scale-up on HCV micro-elimination among PLWH in San Diego County.
**Methods:** A dynamic, compartmental model of HCV transmission among key populations (people who inject drugs and men who have sex with men) was developed and calibrated to data for San Diego County, California. The model was stratified by age [18-39, 40-54, 55-74, 75+], gender, HCV risk (PWID, former PWID, or MSM), and HIV status. The model is parameterized using the 2018 San Diego County 2018 HCV seroprevalence estimates of 65.6%, 4.6%, and 16.5% among PWID, MSM, and MSM with HIV, respectively. Additionally, we calibrated HCV viremia prevalence among PLWH of 30.9% (2013) and 18.5% (2018) based on the UCSD Owen Clinic data. In 2018, a rapid scale-up of HCV treatment among PLWH occurred at UCSD, but it is unclear whether treatment scale-up was widespread across the county. So, we simulated future impact on HCV incidence with the following scenarios from 2018 onwards: 1) continuation of pre-2018 treatment rates [counterfactual, 16.4% of chronically infected PLWH treated/year], 2) scale-up only at UCSD [average 22.1% chronically infected PLWH treated/year], 3) scale-up across all sites to the levels achieved at UCSD [38.1% chronically infected PWH treated/year].
**Results:** The model predicts 333 new HCV infections among PLWH in 2022, down from 422 in 2015. If pre-2018 treatment rates were continued, HCV incidence among PLWH would only reduce by a relative 33.2% from 2015-2030. The scale-up achieved at UCSD since 2018, if continued, could reduce incidence by an additional 12.1% among PLWH. If scale-up has occurred across the county, incidence could be reduced by an additional 35.3% to 182 new infections by 2030. These reductions in incidence can be tracked through corresponding reductions in viremia prevalence among PLWH (Figure 1b) to monitor elimination progress.

**Conclusion:** San Diego is progressing towards HCV micro-elimination among PLWH, but further scale-up and monitoring of HCV viremia among PLWH are required.

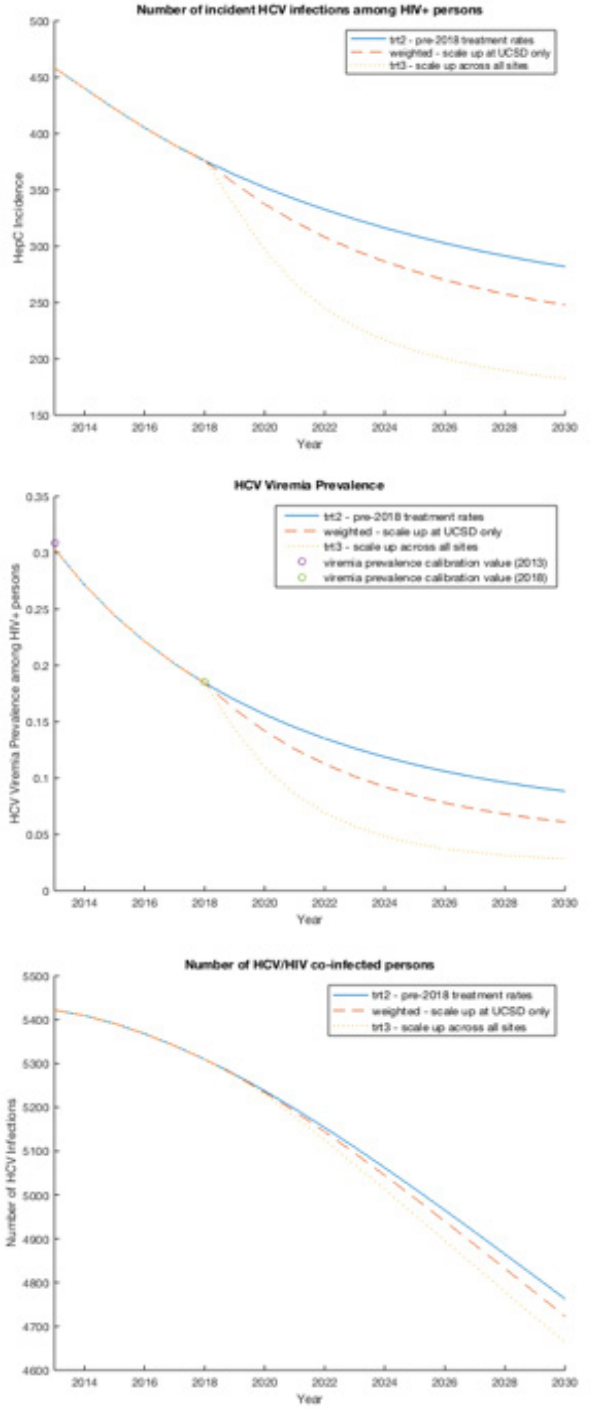



**Figure 1: HCV incidence (a), viremia prevalence (b), and number viremic (c) among PLWH in San Diego.**

## 543 REGIONAL VARIATION IN HBV PREVALENCE IN PEOPLE LIVING WITH HIV IN BOTSWANA

New Investigator Scholar

**Bonolo B. Phinius**[1], Motswedi Anderson[1], Irene Gobe[2], Margaret Mokomane[2], Sharon Mutenga[3], Molly Pretorius Holme[4], Tendani Gaolathe[1], Mompati Mmalane[1], Roger L. Shapiro[4], Joseph Makhema[1], Shahin Lockman[4], Vlad Novitsky[4], Max Essex[4], Sikhulile Moyo[1], Simani Gaseitsiwe[1]

*[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]University of Botswana, Gaborone, Botswana, [3]Midlands State University, Gweru, Zimbabwe, [4]Harvard TH Chan School of Public Health, Boston, MA, USA*

**Background:** Hepatitis B virus (HBV) chronically affects 296 million people worldwide resulting in approximately 820,000 deaths annually. Human immunodeficiency virus (HIV) co-infection increases the risk of HBV disease progression. This study aimed to determine the burden of active HBV in people with HIV (PWH) in a large population-based cohort of rural and peri-urban communities throughout Botswana.

**Methods:** Archived entry-visit samples from PWH who participated in the random 20% household survey of the Botswana Prevention Combination Project (2013-2018) in 30 geographically dispersed villages were screened for various HBV serological markers following the manufacturer's protocols. Plasma samples were first screened for HBV surface antigen (HBsAg) and HBV total core antibodies (anti-HBc). HBsAg positive (HBsAg+) samples were further screened for recent infection by HBV core immunoglobulin M antibody (anti-HBc IgM) and for active infection by HBV e antigen (HBeAg). Risk factors for HBV infection we determined using logistic regression adjusting for age, gender, and clustering by community.

**Results:** Among 3,596 PWH, a total of 2751 (76.5%) PWH were screened for HBsAg and 7.9% [95%CI: 6.9 – 8.9] were positive. Participants with HBV were more likely to be male (OR=1.85; 95%CI: 1.37-2.50). There was an association between HBV prevalence and region (p <0.001). Participants from the northern region were more likely to be HBV infected compared to the those from the south (OR=1.88; 95%CI:1.15 – 2.99). Exposure to HBV (total anti-HBc) was found in 54.2% [95% CI: 51.9 – 56.5] of 1828 tested participants. Among 195 persons with HBsAg+, recent infections (anti-HBV IgM+) were identified in 7.2% [95%CI: 4.3 – 11.7], and all but 1 were on ART. Approximately 13.9% [13.9%, 95% CI: 9.5 – 20.1] of HBsAg+ participants were HBeAg+, indicating active replication; all but 2 were on ART. Of the 15 HBeAg+ participants with ART data, 7/15 (46.7%) individuals with active replication (HBeAg+) were on either tenofovir disoproxil fumarate (TDF), or lamivudine, 7/15 (46.7%) or both, 14/15 (93.3%).

**Conclusion:** HBV prevalence was 7.9% among PWH in Botswana and varied significantly by gender and region. A high proportion of participants were previously exposed to HBV infection, but the majority had cleared the infection at the time of this cross-sectional analysis. Actively replicating virus (HBeAg+) was identified in a small number of individuals despite TDF- and 3TC-containing ART.

**Table 1**: Factors associated with HBV infection

| Characteristics | HBV–infected (HBsAg+) N= 216 | HBV–uninfected (HBsAg-) N= 2535 | *p-value** |
|---|---|---|---|
| **Gender, N (%)** | | | |
| Female | 133 (61.6) | 1897 (74.8) | |
| Male | 83 (38.4) | 638 (25.2) | <0.001 |
| **Age, years, median (IQR)** | 41 (34 – 48) | 40 (33 – 48) | 0.288 |
| **Age, years, N (%)** | | | |
| **<21** | 2 (0.9) | 73 (2.9) | |
| **≥21** | 214 (99.1) | 2462 (97.1) | 0.091 |
| **Region** | | | |
| South | 40 (18.5) | 667 (26.3) | |
| Central | 63 (29.2) | 926 (36.5) | |
| North | 113 (52.3) | 942 (37.2) | <0.001 |
| **CD4, cells/mm$^3$, median (IQR)** | 349 (215 – 493) | 406 (254 – 596) | 0.067 |
| **Log HIV viral load, copies/mL, median (IQR)** | 1.60 (1.60 – 1.64) | 1.60 (1.60 – 2.77) | 0.241 |
| **HIV viral load suppression, N (%) n= 2742** | | | |
| Undetectable | 161 (74.5) | 1778(70.4) | |
| Detectable | 55 (25.5) | 748(29.6) | 0.213 |
| **ART status. n= 2748** | | | |
| Defaulters | 2 (0.9) | 19 (0.8) | |
| ART-naïve | 43 (19.9) | 661 (26.1) | |
| On ART | 171 (79.2) | 1852 (73.1) | 0.132 |
| **Duration on ART, days, Median (IQR)** | 2432 (1719 – 3510) | 2501 (1443 – 3591) | 0.577 |
| **Type of ART, N (%) n= 1567** | | | |
| TDF-containing | 74 (56.1) | 785 (54.7) | |
| 3TC-containing, non-TDF | 52(39.4) | 584 (40.7) | |
| Non TDF, non 3TC-containing | 6 (4.5) | 66 (4.6) | 0.627 |

*P-values obtained using Wilcoxon rank-sum and Chi-square tests for continuous and categorical variables, respectively.

## 544 A RANDOMIZED TRIAL OF HBV REVACCINATION IN MSM BORN IN THE NEONATAL VACCINATION ERA

**Yi-Chia Huang**[1], Hsin-Yun Sun[2], Chia-Wen Li[3], Sung-Hsi Huang[2], Wen-Chun Liu[2], Yi-Ching Su[2], Sui-Yuan Chang[2], Wen-Chien Ko[3], Chien-Ching Hung[2]

*[1]National Taiwan University Hospital Hsin-Chu Branch, Hsinchu, Taiwan, [2]National Taiwan University Hospital, Taipei, Taiwan, [3]National Cheng Kung University Hospital, Tainan, Taiwan*

**Background:** Implementation of universal neonatal vaccination program against hepatitis B virus (HBV) has significantly reduced HBV seroprevalence

in general population and people living with HIV (PLWH). Optimal strategy of revaccination remains unknown among people whose immunity has waned after neonatal vaccination. This randomized controlled trial investigated the serological responses to three standard- (20-µg) or double-dose (40-µg) HBV revaccination among HIV-positive and HIV-negative men who have sex with men (MSM).

**Methods:** MSM who were born after 1 July, 1986 and tested negative for HBsAg and anti-HBc with anti-HBs titer <10 mIU/ml were eligible for enrollment. Subjects who were aged <20 years or receiving chemotherapy or immunosuppressants within 30 days prior to screening were excluded. PLWH not on stable antiretroviral therapy were also excluded. Participants were randomized in a 1:1 ratio (stratified by CD4 count for PLWH) to receive three standard or double doses of HBV vaccine that were administered at Weeks 0, 4, and 24. Adverse events were recorded for severn days after each injection and serological responses were assessed at Weeks 28 and 48. Primary end point was serological response at Week 28 (defined as having anti-HBs titer ≥10 mIU/ml) and secondary end points were high-titer response (anti-HBs ≥100 mIU/ml) and adverse effects.

**Results:** From September 2017 to September 2021, 243 (75%) HIV-positive MSM and 81 (25%) HIV-negative MSM with a mean age of 27.6 years were enrolled with 162 in each arm. The two groups were well balanced in terms of clinical characteristics. In PLWH, 70% had CD4 counts > 500 cells/mm$_3$ and 95% were virally suppressed (HIV RNA load <50 copies/ml). The serological response rates at Week 28 were 95% and 88% for double-dose and standard-dose and double-dose group (p=0.04), respectively; and the respective high-titer response rate was 85% and 75% (p=0.05). At Week 48, the high-titer response rate for double-dose group was higher than that for standard-dose group (88% vs 61%, p=0.025). In multivariate logistic regression analysis (Table), double-dose HBV revaccination and baseline anti-HBs titer were significantly associated with serological response and high-titer response at Week 28 and 48.

**Conclusion:** Revaccination with three double doses of HBV vaccine results in higher serological responses than with three standard-doses of HBV vaccine among MSM who were born in the era of universal neonatal HBV vaccination.

Table. Multivariate logistic regression analysis of factors associated with serological response and high-titer response for all participants

| Week 28 | Serological response (anti-HBs ≥10 mIU/ml) | | High-titer response (anti-HBs ≥100 mIU/ml) | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | P value |
| Dose (double vs standard) | 3.47 (1.18-10.24) | 0.024 | 2.26 (1.12-4.59) | 0.023 |
| Age, per 1-year increase | 0.93 (0.79-1.09) | 0.345 | 0.86 (0.76-0.96) | 0.009 |
| HIV infection (yes vs no) | 1.00 (0.30-3.38) | 0.997 | 1.56 (0.67-3.61) | 0.301 |
| Anti-HBs titer at screening, per 1-mIU/ml increment | 1.48 (1.09-2.02) | 0.012 | 1.77 (1.39-8.19) | <0.001 |
| **Week 48** | **Serological response (anti-HBs ≥10 mIU/ml)** | | **High-titer response (anti-HBs ≥100 mIU/ml)** | |
| | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | P value |
| Dose (double vs standard) | 2.68 (1.09-6.62) | 0.032 | 2.32 (1.24-4.35) | 0.008 |
| Age, per 1-year increase | 0.92 (0.79-1.06) | 0.239 | 0.89 (0.80-0.99) | 0.028 |
| HIV infection (yes vs no) | 0.63 (0.19-2.03) | 0.435 | 0.71 (0.32-1.59) | 0.409 |
| Anti-HBs titer at screening, per 1-mIU/ml increase | 1.46 (1.13-1.90) | 0.004 | 1.49 (1.26-1.76) | <0.001 |

## 545 A LONG-ACTING TENOFOVIR PRODRUG SUPPRESSES HBV REPLICATION FOR OVER 3 MONTHS

New Investigator Scholar

**Srijanee Das**[1], Weimin Wang[1], Denise A. Cobb[1], Murali Ganesan[1], Franchesca G. Fonseca[2], Mohammad Ullah Nayan[1], Suyash Deodhar[1], Brandon Hanson[1], Edward Makarov[1], Howard E. Gendelman[1], Natalia A. Osna[1], Benson J. Edagwa[1], Larisa Y. Poluektova[1]

*[1]University of Nebraska Medical Center, Omaha, NE, USA, [2]University of Nebraska, Omaha, NE, USA*

**Background:** Tenofovir (TFV) prodrugs (TFV alafenamide, TAF and TFV disoproxil fumarate, TDF) are recommended for the treatment of chronic hepatitis B (HBV) in patients with HIV co-infection. However, TAF and TDF exhibit short half-lives and therefore require frequent administration. Consequently, this has resulted in treatment failures mainly due to patient non-adherence. To this end, we transformed TFV into a long-acting prodrug formulation (NM1TFV) and demonstrated sustained active diphosphate metabolite (TFV-DP) levels in key HIV and HBV target cells and tissues of Sprague Dawley rats for up to two months [Nat Commun 12,5458(2021)]. We now demonstrate that a single intramuscular dose of NM1TFV provides sustained efficacy in HBV-infected chimeric liver humanized mice and HBV transgenic Tg05 mice.

**Methods:** A lipophilic TFV prodrug, M1TFV, was synthesized and nanoformulated into stable poloxamer 407 stabilized aqueous nanocrystals (NM1TFV) by high-pressure homogenization. Solid drug nanocrystals of TAF (NTAF) were produced and used as controls. Formulation efficacy was evaluated in two mouse models (HBV-infected humanized liver TK-NOG mice and HBV transgenic Tg05 mice) following a single intramuscular injection of 168 mg/kg TFV equivalents of either NM1TFV or NTAF. HBV DNA levels in peripheral blood were assessed biweekly for 12 weeks. HBV markers HBcAg and HBsAg were evaluated on stained liver sections of TK-NOG mice. Drug levels were quantified by mass spectrometry.

**Results:** NM1TFV suppressed HBV DNA in blood to undetectable levels in all the infected humanized mice over twelve weeks with stable human albumin level (Figure 1). High drug concentrations were recorded at 12 weeks in livers and muscle injection sites of animals treated with NM1TFV. In contrast, NTAF exhibited a limited inhibitory effect on HBV DNA replication levels, consistent with undetectable drug concentrations recorded in the liver at 12 weeks. Notably, the expression of HBcAg and HBsAg was significantly decreased in NM1TFV treated animals compared to NTAF. Enhanced sustained efficacy is also demonstrated for NM1TFV in HBV transgenic mice.

**Conclusion:** Collectively, this work demonstrates that a single intramuscular injection of NM1TFV into infected humanized mice suppresses HBV replication over three months with no notable adverse events.

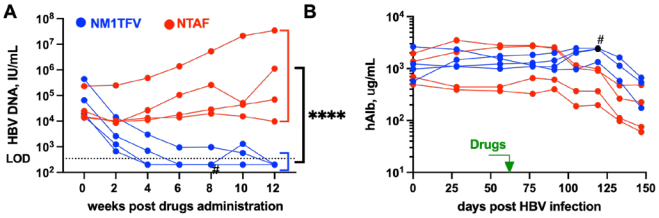



**Figure 1. Suppression of HBV replication in humanized TK-NOG mice. A**, The dynamics of HBV DNA viral load in peripheral blood. NM1TFV suppressed viral replication below the levels of detection (LOD, 350 UI/mL) over 3 months. **B**, The levels of albumin (hAlb) in peripheral blood. Control of HBV replication was not related to loss of human hepatocytes. NTAF was not able to control HBV replication. # - lost mouse but not related to treatment. **** - P<0.0001 by one-way ANOVA between effects of NM1TFV and NTAF.

## 546 LOW RATES OF HEPATITIS B VACCINATION AMONG HIV PATIENTS

**Mamta K. Jain**[1], Karen J. Vigil[2], Onkar Kshirsagar[3], Laura A. Hansen[1], Barbara S. Taylor[4], Mae Thamer[3]

*[1]University of Texas Southwestern, Dallas, TX, USA, [2]University of Texas at Houston, Houston, TX, USA, [3]Medical Technology & Practice Patterns Institute, Bethesda, MD, USA, [4]University of Texas at San Antonio, San Antonio, TX, USA*

**Background:** Hepatitis B is a vaccine-preventable disease. The traditional vaccine series is dosed at 0, 1 and 6 months. We examined 3-dose vaccine regimen completed in a cohort of people with HIV (PWH), since hepatitis B impacts 8-10% of PWH due to the common mode of transmission.

**Methods:** This is a multi-site retrospective study. Inclusion criteria were PWH with 1 to 9 years of follow-up from 1/1/11 to 12/31/18. Patients were excluded if no HIV viral load or CD4 count were available, hepatitis B surface antigen was positive or hepatitis B surface antibody (HBsAb) was "reactive." We examined the outcome after receipt of 3 vaccines over a 12-month period. We also examined the outcome of achieving a reactive HBsAb after completion of the series. Multivariate analysis examined co-variates for the outcomes of receiving 3 doses and of achieving protective immunity.

**Results:** Out of 32,417 PWH, 6,506 were included (69.7% male, 55.7% Black, 55.6% indigent), 40.9% had CD4 <200 cells/µL, 10.3% HIV viral load <50 copies/mL at study entry. Overall, 583 (9%) received 3 doses of vaccine over a 12-month period. Women, non-English speakers, those with hypertension, non-HCC cancers, NAFLD, opportunistic infections, and those with CD4 > 200 cells/µL at baseline were more likely to be fully vaccinated (Table 1). Those less likely to be

vaccinated were those age 45-54 years vs. <34-year-old, Black vs. non-Hispanic White, Medicare vs. commercial insurance, those not on HBV specific medication vs. HBV specific ART, and those with HCV. Of those who received the 3 doses of hepatitis B vaccine and had HepBsAb measured (48%; 281/583), 52% were HBsAb-reactive after 3rd dose. HBsAb-reactive after vaccination was associated with CD4 >200 cells/μL. Hispanic white and those with opportunistic infections were less likely to be immune after vaccination.

**Conclusion:** This study demonstrates that less than 10% of PWH without documented HBsAb+ received 3 doses of hepatitis B vaccine in 12-month time frame, and half of those vaccinated developed protective immunity. Those more likely to complete the series had co-morbidities requiring frequent visits. As expected, those with higher CD4 counts achieved reactive HBsAb, but it is unclear why Hispanics were less likely to achieve reactive HBsAb after vaccination. Higher risk individuals may need additional support or shorter course vaccination series to increase rate of completion.

**Table 1.** Cox Proportional Hazards model of likelihood of vaccination and related outcomes of PWH without documented HepBsAb from 2011 - 2018. *Only significant predictors are presented.*

| | Predictors of receiving 3 HBV vaccines in 1 year period | | | | Predictors of HBsAb immunity | | | |
|---|---|---|---|---|---|---|---|---|
| *Covariate* | aOR | 95% CI | | P value | aOR | 95% CI | | P value |
| Female vs. male | 1.22 | 1.02 | 1.46 | **0.030** | 1.25 | 0.82 | 1.92 | 0.306 |
| | | | | | | | | |
| Hispanic White vs. Non-Hispanic White | 1.08 | 0.84 | 1.37 | 0.556 | 0.55 | 0.30 | 1.00 | **0.050** |
| Black vs. Non-Hispanic White | 0.75 | 0.58 | 0.97 | **0.026** | 0.71 | 0.43 | 1.18 | 0.186 |
| | | | | | | | | |
| Medicare vs. commercial insurance | 0.55 | 0.32 | 0.96 | **0.034** | 1.58 | 0.34 | 7.41 | 0.561 |
| None/Indigent vs. commercial insurance | 1.34 | 1.06 | 1.69 | **0.014** | 0.89 | 0.57 | 1.40 | 0.623 |
| | | | | | | | | |
| Non-English speaking vs. English speaking | 1.96 | 1.55 | 2.48 | **<.0001** | 0.76 | 0.44 | 1.31 | 0.315 |
| | | | | | | | | |
| HCV (yes vs. no) | 0.76 | 0.58 | 1.00 | **0.051** | 0.85 | *0.45* | *1.61* | 0.614 |
| Hypertension (yes vs. no) | 1.41 | 1.08 | 1.83 | **0.011** | 0.82 | *0.46* | *1.46* | 0.500 |
| Non HCC cancers (yes vs. no) | 1.27 | 1.05 | 1.55 | **0.016** | 0.77 | 0.50 | 1.19 | 0.243 |
| NAFLD (yes vs. no) | 1.35 | 1.00 | 1.83 | **0.048** | 0.60 | 0.31 | 1.16 | 0.128 |
| Opportunistic Infections (yes vs. no) | 1.47 | 1.22 | 1.76 | **<.0001** | 0.59 | 0.38 | 0.91 | **0.016** |
| | | | | | | | | |
| CD4+ count > 200 vs. ≤ 200 | 2.19 | 1.80 | 2.66 | **<.0001** | 1.81 | 1.17 | 2.79 | **0.008** |
| | | | | | | | | |
| No HBV specific regimen vs. HBV-specific HIV regimen | 0.46 | 0.35 | 0.60 | **<.0001** | 1.04 | 0.55 | 1.96 | 0.902 |

## 547 HEPATITIS B RNA AND CORE-RELATED ANTIGEN IN HIV-HBV COINFECTION

**Kasha P. Singh**[1], Jennifer Zerbato[1], Wei Zhao[1], Danny K. Wong[2], Gavin Cloherty[3], Jeffrey Gersch[3], Hugh Mason[1], Ajantha Rhodes[1], Peter Revill[1], Anchalee Avihingsanon[4], Jennifer Audsley[1], Man-Fung Yuen[2], Sharon Lewin[1]
*[1]Peter Doherty Institute, Melbourne, Australia, [2]University of Hong Kong, Pok Fu Lam, Hong Kong, [3]Abbott Labs, Abbott Park, IL, USA, [4]Chulalongkorn University, Bangkok, Thailand*

**Background:** HBV core related antigen (HBcrAg) and HBV RNA are potential surrogate markers for intrahepatic HBV covalently closed-circular (ccc)DNA. cccDNA persists in infected hepatocytes despite HBV DNA suppression with antivirals. There are limited data on these markers in people with HIV-HBV co-infection on HBV-active antiviral therapy (ART).

**Methods:** People with HIV-HBV co-infection naïve to ART were recruited in Thailand in a prospective observational study. Liver fibrosis was measured by biopsy and transient elastography (TE) and blood and liver samples obtained pre- and following HBV-active ART. Liver HBV cccDNA was quantified using droplet digital PCR. HBcrAg and HBV RNA were measured in plasma using a chemiluminescence assay and high throughput test respectively. Differences between groups were assessed by Mann-Whitney and correlations by calculation of Spearman's rank correlation coefficients.

**Results:** Participants (n=37) were enrolled and followed for a median of 3.4 years of ART (n=18). They were mainly young men with median CD4+ T cell count pre- and on ART of 360 and 645 cells/μL respectively. At baseline, most had mild liver fibrosis (95% F0/F1 on biopsy) and the median (IQR) TE score was 6.2 (5.2, 8.1) kPa. At baseline and on ART, 61% and 28% were HBeAg positive respectively. cccDNA was quantified in 22 participants at baseline, 11 of them also had follow-up results. HBcrAg and HBV RNA were quantified in 30 at baseline, 17 also had follow-up results. cccDNA, HBcrAg and HBV RNA were lower in HBeAg negative versus positive individuals both pre- and on ART ($p<0.005$ for comparisons). Pairwise comparison of the same participants pre- and on ART showed no change in cccDNA (n=11) or HBV RNA (n=17) while HBcrAg decreased (n=17; p=0.034). Both HBcrAg and HBV RNA correlated with cccDNA pre-ART (n=22, HBcrAg r=0.67, p=0.001; HBV RNA r=0.76, $p<0.0001$). Pre-ART HBV RNA correlated with cccDNA in eAg positive participants (n=16, r=0.54, p=0.041). In eAg negative participants cccDNA was negative in 5/6 (3 also had negative HBV RNA). On ART both HBcrAg and HBV RNA correlated with cccDNA (n=17; HBcrAg r=0.81, $p<0.0001$; HBV RNA r=0.77, p=0.0002) and in the HBeAg negative subset (n=12; HBcrAg r=0.58, p=0.042; HBV RNA r=0.59,p=0.046).

**Conclusion:** Following HBV-active ART in people living with HIV-HBV co-infection, there is no change in cccDNA or HBV RNA. On ART both HBV RNA and HBcrAg correlate with cccDNA including amongst HBeAg negative participants, consistent with findings in HBV monoinfection.

## 548 NEW HEPATITIS B INFECTION AMONG HIV PATIENTS: WHO IS AT RISK?

**Mamta K. Jain**[1], Karen J. Vigil[2], Onkar Kshirsagar[3], Laura A. Hansen[1], Barbara S. Taylor[4], Mae Thamer[5]
*[1]University of Texas Southwestern, Dallas, TX, USA, [2]University of Texas at Houston, Houston, TX, USA, [3]Academic Medical Center, Amsterdam, Netherlands, [4]University of Texas at San Antonio, San Antonio, TX, USA, [5]Medical Technology & Practice Patterns Institute, Bethesda, MD, USA*

**Background:** New hepatitis B infection is infrequent but preventable. Vaccines and hepatitis B virus (HBV) specific antiretrovirals (ART) may offer protection for people living with HIV (PLWH). Hepatitis B in PLWH places them at increased risk for mortality compared to PLWH without HBV or those with HBV alone. We sought to examine the incidence of HBV and factors which predict risk for acquiring infection among PLWH.

**Methods:** This is a multi-site retrospective study. Inclusion criteria were PLWH with minimum of 1 up to 9 years of follow-up from 1/1/11 to 12/31/18. Patients were excluded if no HIV viral load or CD4 count were available. We excluded those who were hepatitis B surface antigen (HepBsAg) positive within 6 months of study entry or 1 year after; hepatitis B e antigen positive, or HBV DNA positive within first 6 months prior to study entry. We examined the outcome of becoming HepBsAg positive in the follow-up period.

**Results:** Out of 26, 152 PLWH, 12,285 were included (72.3% male, 56.9% Black, 58.7% indigent), 35.2% had CD4 <200 cells/μL, 12.3% HIV viral load <50 copies/mL, 42.6% were HBV immune at study entry. Within 2 years of study entry, 80.6% were on an HBV-specific HIV regimen. Overall, 0.49% (n= 60, 70% male, 77% Black; 65% non-immune and 52% with CD4 <200 cell/μL at baseline) developed incident hepatitis B during follow-up. Those with HCV (aOR 3.08 95% CI: 1.72-5.51, p<.01), non-HCC cancers (aOR 1.96, 95% CI: 1.13-3.42, p=0.02), or HBsAb non-immune at baseline (aOR 4.56 95% CI: 2.11-9.86, p<.01) were more likely to develop new hepatitis B infection. Being on non-HBV specific medication or not on ART vs. being on HBV specific regimen at baseline (aOR 1.17 95% CI: 0.06-2.25, p=0.65) was not associated with new HBV infection. Figure 1 shows cumulative risk of acquiring incident HBV stratified by HCV status and hepatitis B immune status.

**Conclusion:** Patients who are not vaccinated against hepatitis B are at increased risk for HBV infection. We found a high risk for incident HBV among those with hepatitis C and those with non-HCC cancers, which may be associated with other risk factors for hepatitis B transmission. We did not observe a protective effect of HBV specific medication at baseline for development of new HBV infection in follow-up. Understanding the etiology of new hepatitis B infection in the HIV population is essential in designing future effective target programs for hepatitis B elimination among this vulnerable population.

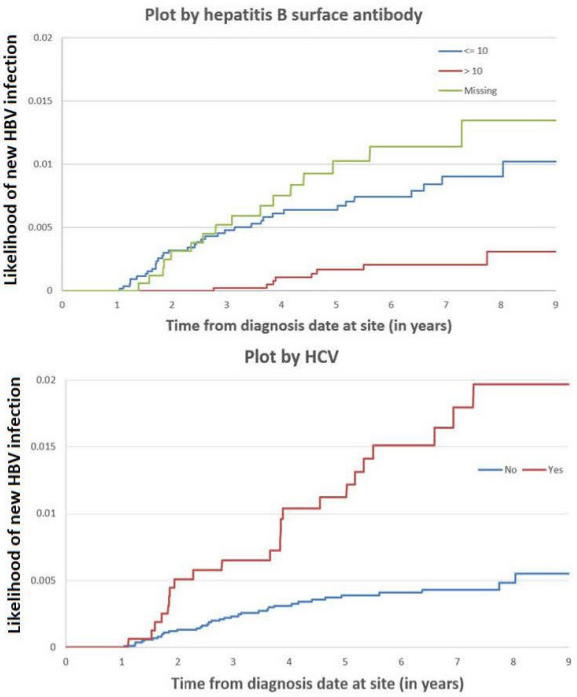



Figure 1. Cumulative Kaplan-Meier Plots by hepatitis B surface antibody (top) and HCV status (bottom); all differences are Log rank $p$< .0001.

## 549 ETIOLOGY OF LIVER DISEASE IN ADULTS WITH HIV IN LOW- AND MIDDLE-INCOME COUNTRIES

**Marie K. Plaisy**[1], Albert Minga[2], Gilles Wandeler[3], Alain Attia[4], Renee De Waal[5], Jeremy Ross[6], Niha Samala[7], Sonia Salvi[8], Mark H. Kuniholm[9], Gad Murenzi[10], Hugo Perrazo[11], Antoine Jaquet[1]

*[1]University of Bordeaux, Inserm, French National Research Institute for Sustainable Development (IRD), UMR 1219, Bordeaux, France, [2]Blood Bank Medical Center, the HIV care clinic of the National Blood Transfusion Center, Abidjan, Cote d'Ivoire, [3]Institute of Social and Preventive Medicine, Bern, Switzerland, [4]University Hospital Yopougon, Abidjan, Cote d'Ivoire, [5]Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa, [6]TREAT Asia, amfAR, Bangkok, Thailand, [7]Indiana University, Indianapolis, IN, USA, [8]Byramjee Jeejeebhoy Government Medical College, Pune, India, [9]University at Albany, State University of New York, Rensselaer, NY, USA, [10]Rwanda Military Hospital and Research for Development, Kigali, Rwanda, [11]National Institute of Infectious Diseases Evandro Chagas-Oswaldo Cruz Foundation (INI/FIOCRUZ), Rio de Janeiro, Brazil*

**Background:** In high-income countries, liver disease represents a growing cause of morbidity and mortality among people living with HIV (PLHIV), and is linked to an increased burden of metabolic disorders. Little is known about the contribution of non-communicable diseases to the burden of liver disease in low and middle-income countries (LMIC).

**Methods:** We conducted a cross-sectional analysis of data collected between June 2015 and August 2021 from two ongoing cohorts: IeDEA-Sentinel Research Network and PROSPEC, which include PLHIV ≥40 years on antiretroviral treatment for ≥6 months in Brazil, Côte d'Ivoire, India, Kenya, Rwanda and Zambia. Patients were screened for hepatitis B and C virus infections (HBsAg, HCV Ab/RNA), obesity, dyslipidemia, hypertension, and diabetes. Alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT). Transient elastography for Liver Stiffness Measurement (LSM)/Controlled Attenuation Parameter (CAP) was performed. Liver fibrosis and steatosis were defined as LSM >7.0 kPa and CAP ≥248 dB/m, respectively. Factors associated with liver fibrosis and steatosis were assessed using multivariate logistic regression models. Population Attributable Fraction (PAF) for liver fibrosis was estimated using Levin's formula.

**Results:** In total, 1,632 PLHIV (58.9% female, median age 50 (interquartile range: 45-52) years) were included in the analysis. Patients were reported to have obesity (19.5%), diabetes (11.3%), hypertension (24.9%), dyslipidemia (53.9%), hepatitis B (4.5%) and C (3.4%). Among PLHIV co-infected with hepatitis B, 67.6% were currently on tenofovir. Hazardous alcohol use (AUDIT score ≥8) was found in 246 (15.1%) patients. LSM and CAP were deemed reliable in 91% (n=1492) and 78% (n=1279) of measurements, respectively. The prevalence of liver fibrosis was 11.7% (95% confidence interval (CI) 10.0-13.9), and 31.3% (CI 28.7-33.8) had steatosis. Hepatitis, male sex, obesity, diabetes and CD4 count <200 cells/mm$_3$ were independently associated with liver fibrosis (see table). Factors associated with steatosis included obesity (OR 5.29, CI 3.46-8.08) and diabetes (OR 2.42, CI 1.58-3.69).

**Conclusion:** Metabolic disorders contributed to a higher proportion of liver fibrosis than chronic viral hepatitis among PLHIV in this LMIC cohort. As access to effective antiviral therapies against chronic viral hepatitis expands, preventive measures against diabetes and obesity in PLHIV are urgently needed.

**Table. Factors associated with liver fibrosis in PLHIV in care at referral HIV clinics in Brazil, Côte d'Ivoire, India, Kenya, Rwanda, and Zambia (n = 1,492)***

| | Univariate analysis | | Multivariate analysis | | PAF, % |
|---|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value | |
| **Age (per 10 years)** | 1.28 (1.04,1.58) | 0.02 | | | |
| **Sex** (males vs females) | 1.94 (1.41-2.67) | <0.001 | 1.51 (1.06-2.17) | 0.02 | |
| **Metabolic features** | | | | | |
| Obesity (BMI >30 Kg/m²) | 2.09 (1.41-3.09) | <0.001 | 2.47 (1.55-3.94) | <0.001 | 17 |
| Type 2 diabetes | 3.76 (2.55-5.54) | <0.001 | 2.56 (1.67-3.94) | <0.001 | 12 |
| Dyslipidemia | 1.24 (0.89-1.73) | <0.001 | | | |
| Hypertension | 1.21 (0.85,1.72) | 0.29 | | | |
| **CD4 count** (<200 cells/mm³) | 1.78 (1.07-2.97) | 0.008 | 2.22 (1.27-4.12) | 0.02 | |
| **Country** | | < 0.001 | | <0.001 | |
| Zambia | 1 | | 1 | | |
| Brazil | 4.93 (2.33-10.46) | | 3.0(1.37-6.58) | | |
| Côte d'Ivoire | 1.64 (0.72-3.73) | | 1.34 (0.58-3.09) | | |
| India | 4.15 (1.84-9.36) | | 3.88 (1.67-8.99) | | |
| Kenya | 0.10 (0.01-0.81) | | 0.10 (0.01-0.82) | | |
| Rwanda | 1.17 (0.50-2.70) | | 1.19 (0.51-2.78) | | |
| **Chronic viral hepatitis markers** | | | | | |
| Positive HBs Ag | 1.82 (0.97-3.4) | 0.06 | 1.87 (0.93-3.76) | 0.07 | 3 |
| Positive HCV Ab/RNA | 9.17 (5.26-15.98) | <0.001 | 5.57 (2.97-10.46) | <0.001 | 8 |
| **AUDIT** Score ≥8** | 0.91 (0.27-3.05) | 0.42 | | | |

*PLHIV with reliable LSM measures out of the 1,632 patients. **≥8 for men and ≥7 for women.

## 550 SINGLE-CELL ANALYSIS OF THE LIVER IN HIV REVEALS PROFIBROTIC MONOCYTES/MACROPHAGES

**Christopher Oetheimer**[1], Michael S. Wallace[1], Alex S. Genshaft[2], Ira Fleming[2], Mike Vilme[2], Lai Ping Wong[1], Michael L. Dadoine[1], Eliana T. Epstein[1], Adaeze Obinelo[1], Ashraf Thabet[1], Alex K. Shalek[2], Ruslan Sadreyev[1], Gregory K. Robbins[1], Raymond T. Chung[1], Nadia Alatrakchi[1]

*[1]Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA*

**Background:** Progression to advanced liver disease in patients with chronic liver inflammation and HIV infection remains a major public health problem despite effective antiretroviral therapy (ART). Monocyte and macrophage populations play a central role in inflammation and liver pathogenesis and are triggered in the setting of HIV. To understand how HIV mono-infection and ART modulate these cells in the liver, we characterize their single-cell (sc) transcriptome in peripheral blood, and for the first time in the liver using fine-needle aspirations (FNA).

**Methods:** Liver FNA cells and corresponding peripheral blood mononuclear cells (PBMC) from 7 patients with HIV infection, at baseline and after 6-months of ART, were analyzed using the scRNA-sequencing Seq-Well approach.

**Results:** Transcriptome profiling of 6,629 FNA and 8,203 PBMC showed a significant amelioration of naïve CD4+ T cells, a decrease in CD8+ effector memory T cells, and a decrease in monocyte interferon-related gene signature (ISGs) upon virus control in PBMC, confirming the study model. Interestingly, downregulation of ISGs in monocytes was also observed in the liver, supporting HIV's impact on the liver milieu. Monocyte and macrophage populations (852 FNA and 868 PBMC) revealed gene expression differences between the 2 compartments and a heterogeneity associated with distinct functional roles. In both compartments, we uncovered 1) presence of monocytic myeloid-derived suppressor cells (MDSC) which persisted upon ART despite virus control. MDSCs have been shown to suppress T cell responses and generate profibrotic M2 macrophages; 2) presence of heterogeneous macrophage populations, which expressed CD5L and became undetectable upon ART. Interestingly, secreted levels of the macrophage-derived and profibrotic product CD5L were high at baseline and surprisingly did not decrease on ART, suggesting continuous macrophage activity.

**Conclusion:** Our data underscore the complexity of monocyte and macrophage populations and suggest their involvement in generating a profibrotic milieu in the liver during HIV infection which is only partially reversed with initiation of ART. This could explain the progression of liver disease in the context of HIV infection, even with viral suppression.

## 551 CDA/CD8 RATIO ≥0.5 IS A RISK FACTOR OF ACUTE REJECTION IN HIV-INFECTED LT RECIPIENTS

**Sandra Silva Arrieta**[1], Lucia Serrano[2], Antonio Rafecas[3], Christian Manzardo[4], Jesus Fortun[5], Marino Blanes[6], Magdalena Salcedo[7], Itxarone Bilbao[8], Elisa Cordero[9], Santos Del Campo[5], Asuncion Moreno[4], Antonio Rimola[4], Christian Brander[1], Jose M. Miro[4]

*[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Fundación SEIMC-GeSIDA, Madrid, Spain, [3]Hospital Universitario de Bellvitge, Barcelona, Spain, [4]Hospital Clinic of Barcelona, Barcelona, Spain, [5]Hospital Ramón y Cajal, Madrid, Spain, [6]Hospital la Fe, Valencia, Spain, [7]Hospital Gregorio Marañón, Madrid, Spain, [8]Hospital Universitario Vall d'Hebrón, Barcelona, Spain, [9]Hospital Universitario Virgen del Rocio, Sevilla, Spain*

**Background:** HIV-infected liver transplant (LT) recipients have higher rates of acute rejection than uninfected recipients. Previously we identified host and donor genetic markers (HLA class I and II mismatches and interferon-λ3 and -λ4 gene polymorphisms) that can increase the risk of organ-rejection in HCV/HIV LT recipients. However, HIV-related factors of acute rejection have been poorly studied. We investigated whether virological and immunological status and type of antiretroviral therapy influence acute-rejection risk in HIV-infected LT recipients.

**Methods:** 272 consecutive HIV-infected patients undergoing LT from 2002–2012, then followed until December 2019, in 22 Spanish medical centers were included. All acute-rejection episodes were biopsy-proven. Acute-rejection prognostic-factor analysis was done using Cox proportional hazards model. Statistical analysis was done in SPSS 24.0.

**Results:** Median (IQR) age was 46 years (42-49); 78% of patients were male. Former IV drug use (74%) was the most frequent HIV risk factor. The etiology of end-stage liver disease was co-infection with HCV (80%), HBV (5%), HCV/HBV (11%) and non-viral etiology (4%). 20% of cases were cured of HCV pre-LT. Hepatocellular carcinoma was diagnosed in 27% of cases. At pre-LT, median (IQR) MELD was 15 (11;20) and CD4+T cell count was 277 (176;414) cells/mm$_3$. CD4/CD8 ratio was ≥0.5 in 77% of cases. 93% of patients had suppressed HIV viremia (VL<200 copies/mL) on ART. Median (IQR) donor risk index was 1.6 (1.3; 1.9) and 35% of donors were ≥60 years. Initial immunosuppression was cyclosporin- and tacrolimus-based in 30% and 58% of cases, respectively. Post-LT ART was started after a median (IQR) of 7 (4;16) days and was based on raltegravir in 22% of cases. 72 (26%) recipients developed an acute rejection episode within the first 48 weeks post-LT. Median (IQR) time to acute rejection was 13.0 (10.0; 25.0) days. Donor and recipient age, pre-LT CD4/CD8 ratio ≥0.5, time to restart ART post-LT and RAL-based ART were independently associated with acute rejection (Table). Patients with CD4/CD8 ratio ≥0.5 had >3 times greater acute-rejection risk. This variable was also identified when focusing analysis only on HCV/HIV LT recipients (HR [95%CI] 5.02 [1.53; 16.52]).

**Conclusion:** Three HIV-infection related factors, namely CD4/CD8 ratio, time to restart ART post-LT and raltegravir-based ART are associated with acute rejection. These findings may help improve post-LT management in HIV-infected recipients.

**Table: Risk factors for acute rejection**

| Variables | Univariate (HR 95% CI); p-value | Multivariate (HR 95% CI); p-value |
|---|---|---|
| Calendar year (before 2007) | 1.94 (1.22; 3.09); 0.005 | |
| Recipient age (per year increase) | 0.96 (0.93;1.00); 0.052 | 0.95 (0.91;0.99); 0.047 |
| Gender (female) | 1.07 (0.62;1.84); 0.813 | |
| Pre-LT CD4/CD8 ≥0.5 | 1.65 (0.81; 3.35); 0.165 | 3.29 (1.31;8.27); 0.011 |
| Donor risk index (per unit increase) | 1.08 (0.67;1.73); 0.751 | |
| Donor age ≥60 | 1.54 (0.92; 2.56); 0.097 | 2.63 (1.44;4.83); 0.002 |
| Post-LT ART (RAL-based) | 0.47 (0.23;0.94); 0.033 | 0.36 (0.14;0.94); 0.036 |
| Time to restart ART (per day increase) | 1.02 (1.01;1.04); 0.004 | 1.03 (1.00;1.05); 0.028 |
| HIV duration, HIV risk factors, BMI, AIDS defining events; MELD score, Child score; pre-LT ART type; HIV viral load suppression, waiting list time, donor cause of death, cold ischemia time, type of immunosuppression and HCV etiology were not associated with acute rejection. | | |

## 552 DISTINCT CANCERS HAVE DISTINCT INFLAMMATORY PREDICTORS IN TREATED HIV

**Samuel R. Schnittman**[1], Gabriele B. Beck-Engeser[2], Dave Glidden[2], Robin M. Nance[3], Vanessa York[2], Joseph A. Delaney[4], Amelia N. Deitchman[2], Fran Aweeka[2], Judy K. Shigenaga[2], Michael Saag[5], Carl Grunfeld[2], Franklin W. Huang[2], Heidi Crane[3], Peter W. Hunt[2]

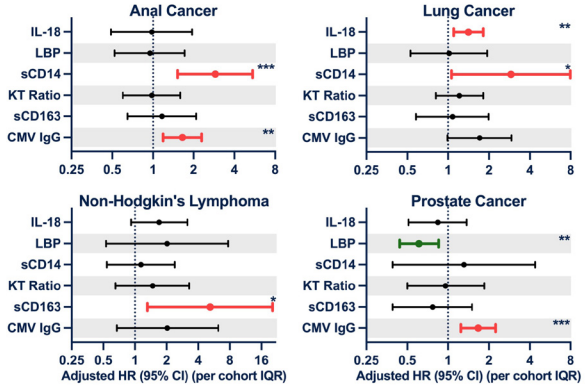
*[1]Massachusetts General Hospital, Boston, MA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]University of Washington, Seattle, WA, USA, [4]University of Manitoba, Winnipeg, Canada, [5]University of Alabama at Birmingham, Birmingham, AL, USA*

**Background:** Despite antiretroviral therapy (ART), people with HIV (PWH) are at higher risk for infection-related and lung cancers and lower risk for prostate cancer than the general population. The inflammatory pathways that may contribute to these risks are incompletely characterized.

**Methods:** Using a case-cohort design, a random sample of all CNICS participants with available plasma during ≥6 months of ART-mediated viral suppression was selected. Among eligible participants, all those subsequently diagnosed with anal, non-Hodgkin's Lymphoma (NHL), lung, or prostate cancer were also sampled. The relationship between 6 plasma biomarkers, log$_{10}$-transformed and normalized to the cohort interquartile range (IQR), and each incident cancer was assessed by multivariate Cox proportional hazards modeling with inverse probability sampling weights based on cohort versus event status, adjusting for age, sex, and smoking history.

**Results:** Of an eligible cohort of 9,340, we sampled a random sub-cohort of 968 participants and 36 anal, 37 lung, and 36 prostate cancer cases and 19 non-Hodgkin's Lymphoma cases, occurring at a median of 4 (IQR 2-6) years following the plasma sample. The sub-cohort had a median age of 47, 83% were men, 29% had a history of smoking, and the median current and nadir CD4 were 573 and 245, respectively. After adjustment, every IQR increase in sCD14 and CMV IgG titer was associated with a 2.9- and 1.7-fold increased hazard of anal cancer (P=0.001, P=0.003, Figure). Every IQR increase in IL-18 (a biomarker of IL-1β signaling) and sCD14 was associated with a 1.4- and 2.9-fold increased hazard of lung cancer (P=0.008, P=0.04). Each IQR increase in sCD163 was associated with a 5.2-fold increased hazard of NHL (P=0.02). Finally, each IQR increase in CMV IgG titer was associated with a 1.7-fold increased hazard or prostate cancer (P<0.001), while LPS binding protein (LBP) was associated with a reduced risk (aHR=0.61, P=0.003).

**Conclusion:** Distinct patterns of inflammation predict different types of cancer in treated HIV, suggesting that interventions targeting discrete inflammatory pathways in this setting are likely to affect risks of some cancers more than others. Nevertheless, CMV IgG titer tended to predict most cancers, potentially suggesting a broader impact of CMV or related exposures on cancer risk in this setting. LBP's association with decreased prostate cancer risk may reflect previously reported LPS- and/or inflammation-mediated suppression of testosterone levels.




## 553 PROINFLAMMATORY GLYCOMIC DYSREGULATIONS PRECEDE CANCER ONSET DURING HIV INFECTION

**Leila B. Giron**[1], Jane Koshy[1], Jianyi Ding[1], David Lu[2], Geoffrey A. Feret[3], Ted Barrell[3], Alan Landay[4], Qin Liu[1], Robert Gross[5], Mohamed Abdel-Mohsen[1]

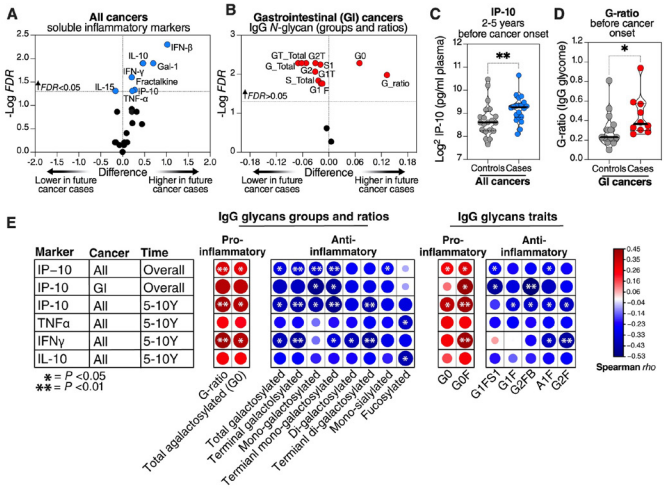
*[1]Wistar Institute, Philadelphia, PA, USA, [2]Cornell University, Ithaca, NY, USA, [3]University of Pennsylvania, Philadelphia, PA, USA, [4]Rush University, Chicago, IL, USA, [5]Hospital of the University of Pennsylvania, Philadelphia, PA, USA*

**Background:** In the general population, host glycomic alterations, in particular, loss of galactose (agalactosylation; measured as high levels of G-ratio and G0 glycan groups), on circulating IgG, drive inflammation and precede the onset of premature aging-associated diseases. We investigated whether glycomic alterations, in particular agalactosylation, precede the development of non-AIDS-defining cancers during antiretroviral therapy (ART)-suppressed HIV infection.

**Methods:** In a longitudinal case-control study, 104 plasma samples were collected between 13.8 and -0.8 years before the onset of cancer in 29 HIV+ ART+ cases; 10 with gastrointestinal (GI) cancers, 9 with skin cancers, and 10 with other non-AIDS-defining cancers. Control samples (121) were collected, at same time-points as cases, from 32 matched (for age at sample collection, sex, and ethnicity) HIV+ ART+ controls without cancers. IgG glycosylation was profiled using capillary electrophoresis, and soluble markers of inflammation were measured by multiplex cytokine arrays. Mann–Whitney and Spearman's rank tests were used for statistical analyses. False discovery rates (FDR) were calculated to account for multiple comparisons.

**Results:** Several markers of inflammation (including IFN-β, IFN-γ, IP-10, IL-10, and galectin-1) were higher in cases (before cancer onset) compared to controls (FDR<0.05; Fig 1A). No differences were observed in G-ratio or G0 glycans between cases and controls when considering all cancers; however, levels of G-ratio and G0 were significantly higher in cases with GI cancers compared to controls (FDR<0.01; Fig 1B). Differences in soluble inflammatory markers between cases and controls were observed 2-5 years before cancer onset (example in Fig 1C; P<0.01). Differences in G-ratio and G0 between GI cancer cases and controls were observed 5-10 years before cancer onset (Fig 1D; P<0.05). Finally, pro-inflammatory IgG glycans correlated with higher inflammation (Fig 1E; P<0.05), whereas anti-inflammatory IgG glycans correlated with lower inflammation (Fig 1E; P<0.05).

**Conclusion:** Our exploratory study suggests that premature-aging-associated glycomic dysregulations and pro-inflammatory responses may precede the onset of non-AIDS-defining cancers, especially inflammation-associated cancers such as GI cancers, during ART+ HIV infection. Potential glycomic and inflammatory pathways fostering cancer progression, during ART-suppressed HIV infection, warrant further investigation into their prognostic and functional significance.




## 554 USING NEXT-GENERATION SEQUENCING TO DETECT GENES RELATED TO CANCER IN WOMEN WITH HIV

**Stephanie Jo**[1], Alicia Golembieski[2], Dwayne Baxa[1]
*[1]Oakland University, Rochester, MI, USA, [2]Henry Ford Hospital, Detroit, MI, USA*

**Background:** Next Generation Sequencing (NGS) is a tool used to detect HIV resistance mutations at a frequency down to 1% of the viral population. It was observed that DNA sequences not aligning to the viral genome were being detected in the sequence pool, and may indicate upregulated host transcripts circulating in the patient plasma. Previous studies have shown that HIV proviral DNA preferentially integrates into genes that are actively expressed including those that promote cell proliferation, and people infected with HIV have an increased risk for cancer compared to the general population. The hypothesis of this study is that upregulated plasma RNA relevant to cancer progression may be detected in patient plasma by NGS testing. The results of this study may help develop HIV resistance testing by NGS to be considered for further evaluation as a screen for the potential of cancer development in patients with HIV.

**Methods:** Non-HIV aligning DNA sequences from 11 random HIV+ females obtained during routine NGS testing for antiretroviral resistance were analyzed via Basic Local Alignment Search Tool (BLAST) for the presence of human genes. Only sequences with 95% homology or greater to genes related to cellular proliferation and disease processes were considered. The matches were evaluated for known correlation with malignancy or cell cycle genes related to tumorigenesis. Patient medical record data was reviewed for the following: cancer diagnoses, cancer type, test orders relevant to suspicion of cancer, general demographics, appointments made with oncology, history of other opportunistic infections and was matched with the information from the BLAST data (Table 1).

**Results:** BLAST results of patients' plasma RNA transcripts identified presence of human genes with known roles in cellular proliferation in all 11 patients as well as sequences related to malignancies. Sequences from one patient included genes related to lung cancer and tumorigenesis and was found to have been diagnosed with adenocarcinoma of the lung (Patient 5, Table 1). While other patients had sequences for tumorigenic genes, the manifestations were less direct.

**Conclusion:** A significant number of human genes were detected in the non-aligning sequences from viral NGS. Further analysis is required to test significance of this correlation.

| Patient | Age Range | Years Since HIV Diagnosis | CD4+ Count (cells/mm³) | Viral Load (RNA copies/mL) | Cancer History (calculated years between HIV diagnosis and pathology result) | Genes Detected |
|---|---|---|---|---|---|---|
| 1 | 50-59 | 7 | 862 | Unknown | Abnormal breast ultrasound (5), colon polyps, mass on back | Ectopic viral integration site 5 |
| 2 | 40-49 | 12 | 370 | 3070 | Cervical cancer (8) | Phospholipase C like 2, Platelet activating factor acetylhydrolase 1b regulatory subunit 1, Interleukin 3 receptor subunit alpha, Centrosomal protein 85 like, Myosin X, LINE1 type transposase domain containing 1, DDB1 and CUL4 associated factor 12 |
| 3 | 20-29 | 5 | 174 | 126 | CIN I (4) | Amyloid beta precursor protein binding protein 2, Zinc Finger MIZ-Type Containing 1 |
| 4 | 30-39 | 22 | 46 | 27322 | | Chromosome 6 ORF 106 |
| 5 | 50-59 | 8 | 122 | 75692 | Adenocarcinoma of lung (7) | Zinc Finger MIZ-Type Containing 1, Deleted In Lymphocytic Leukemia 1, Zinc finger protein 875, Metastasis associated lung adenocarcinoma transcript 1, Negative regulator of ubiquitin like proteins 1 , Ecdysoneless cell cycle regulator, Fc fragment of IgM receptor |
| 6 | 40-49 | 4 | 52 | 1756138 | | Malic enzyme 3 |
| 7 | 30-39 | 3 | 1515 | 21643 | | Rho GTPase activating protein 39, Dual specificity phosphatase 5 pseudogene 1 |
| 8 | 20-29 | 7 | 26 | 1192 | | Zinc Finger MIZ-Type Containing 1, Vav guanine nucleotide exchange factor 2, IQ motif and Sec7 domain 1, CDS8, GFAP, Secreted protein acidic and cysteine rich, ADP dependent glucokinase |
| 9 | 50-59 | 1 | 212 | 86028 | Skin cancer, basal cell carcinoma (1) | ADP dependent glucokinase, Zinc Finger MIZ-Type Containing 1, POU class 4 homeobox 1, Leukocyte immunoglobulin like receptor A3, Sirtuin 5, Homo sapiens P2Y receptor family member 8 |
| 10 | 50-59 | 25 | 229 | <20 | Abnormal pap smear (23), likely cystic lesion on neck (23) | Zinc Finger MIZ-Type Containing 1, Heat shock protein family A (Hsp70) member 9, Rho GTPase activating protein 30 |
| 11 | 50-59 | 30 | 386 | 89 | | Zinc Finger MIZ-Type Containing 1, Adenosine deaminase RNA specific, C1q/tumor necrosis factor-related protein-1, Nuclear factor, erythroid 2 like 1 |

**Table 1: Demographics, HIV History, Labs, Cancer History of Patients, and Relevant Genes Detected.** All 11 patients were randomly selected HIV+ females currently undergoing therapy. CD4+ count and viral load values are those with the closest proximity to the date of the blood draw for the viral genotype. This information was matched with results from BLAST to identify any correlation between genes detected and the development of malignancies. The genes detected only lists genes with known roles in cell cycle regulation and/or tumorigenesis based on literature review. Empty boxes indicated no known history.

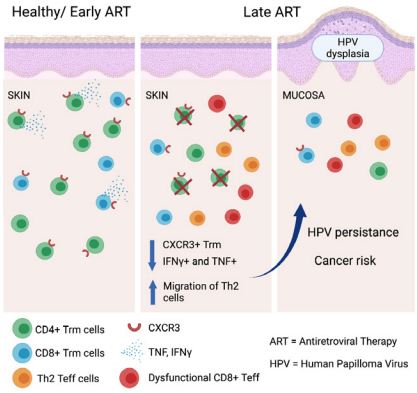
## 555 DELAYED ART LEADS TO IRREVERSIBLE DEPLETION OF SKIN AND MUCOSA RESIDENT MEMORY T CELL

**Simona Saluzzo**[1], Ram Vinay Pandey[1], Laura M. Gail[1], Lisa Kleissl[1], Johanna Strobl[1], Veronique Touzeau-Römer[1], Armin Rieger[1], Matthias Farlik[1], Wolfgang Weninger[1], Georg Stingl[1], Georg Stary[1]
*[1]Medical University of Vienna, Vienna, Austria*

**Background:** People living with HIV (PLWH) are at increased risk of developing skin and mucosal malignancies despite systemic reconstitution of CD4+ T cells upon antiretroviral therapy (ART). The underlying mechanism of chronic tissue-related immunodeficiency in HIV is unclear.

**Methods:** We collected longitudinal skin biopsies and blood samples from early-presenting HIV+ individuals (HIV-EA) before and after one year of ART and compared them to HIV late presenters (HIV-LA) with initial low systemic levels of CD4+ T cells. We compared results with skin and blood from healthy controls We performed single cell RNA sequencing (scRNA-Seq) coupled with TCR sequencing (scTCR-Seq) from blood and skin to follow the dynamics of skin and blood circulating Trm during HIV infection. We additionally performed stainigns for Trm in the skin using Tissue FaXS and automated in situ analysis. We performed flow citometry and in vitro stimulation of skin resident Trm in HIV+ patients and healthy individuals. We selected an additional cohort of patients with HPV-related anal intraepitheliel neoplasia (AIN) that were HIV+ and compared them to HIV negative individuals with the same degree of AIN and analyzed the number of mucosal Trm.

**Results:** We found that skin CD4+ tissue-resident memory T (Trm) cells were depleted after HIV infection and replenished only upon early ART initiation. TCR clonal analysis following early ART suggested a systemic origin for reconstituting CD4+ Trm cells. Single-cell RNA-sequencing of PLWH that received late ART treatment revealed a loss of CXCR3+ Trm cells and a tolerogenic skin immune environment. In biopsies of human papilloma virus-induced precancerous lesions, the frequency of CXCR3+ Trm cells in the mucosa was reduced in PLWH versus HIV- individuals.
**Conclusion:** These results reveal an irreversible loss of CXCR3+ Trm cells confined to skin and mucosa in PLWH that received late ART treatment, which may be a precipitating factor in the development of HPV-related cancer.




## 556 CD4+ AND RISK OF ADVERSE EVENTS IN PARTICIPANTS RECEIVING IMMUNOTHERAPY FOR CANCER

**Thomas Odeny**[1], Kathryn Lurain[1], Julius Strauss[1], Thomas S. Uldrick[2], Steven Fling[2], Elad Sharon[1], Anna K. Wright[2], James Gulley[1], Robert Yarchoan[1], Ramya Ramaswami[1]
*[1]National Institutes of Health, Bethesda, MD, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

**Background:** The Food and Drug Administration recommends that patients with HIV (PWH) with a CD4+ T cell count (CD4) ≥350 cells/μL should generally be eligible for any cancer clinical trial, but there has been a reluctance to enter patients with lower CD4 counts. Patients with relapsed or refractory cancers may also have low CD4 due to prior cancer therapies, irrespective of HIV status. Prospective studies have shown immune checkpoint inhibitors (ICI) are safe among PWH with advanced cancer receiving antiretroviral therapy and CD4 >100 cells/μL. It is unclear whether there is a difference in the proportion of treatment-emergent adverse events (TEAE) and whether this is affected by CD4 count among participants receiving ICI with and without HIV.
**Methods:** We conducted a retrospective cohort study of participants who received ICI for advanced cancers in 2 trials in the US (1 specifically in PWH with CD4 >100). We aimed to compare the proportion of TEAE between PWH and HIV-negative (HIV-) participants and to determine whether the effect of baseline CD4 on incidence of grade ≥3 TEAE was modified by HIV status using a multivariable logistic regression model.
**Results:** Of 102 participants, 46 (45%) were PWH who received pembrolizumab and 56 (55%) were HIV- who received bintrafusp alfa. HIV- participants had relapsed HPV-related malignancies (cervix, anal, head/neck) whereas PWH had both virus- and non-virus-associated cancers. Median CD4 at baseline was 285 cells/uL (IQR 187-495) among PWH and 356 (IQR 260-470) among HIV- participants (p=0.2). Among PWH, 40/46 (87%) experienced any TEAE compared to 43/56 (77%) among HIV- participants. Grade ≥3 TEAE were recorded among 5/46 (11%) PLWH compared to 7/56 (13%) among HIV- participants. When adjusted for age, gender, and ethnicity, the effect of baseline CD4 on incidence of TEAE was not modified by HIV status for any TEAE (interaction term p=0.7), or any grade ≥3 TEAE (interaction term p=0.3). Overall, CD4<350 was not significantly associated with increased risk of any TEAE (aOR 0.12; 95%CI 0.12-1.21; p=0.07) or any grade ≥3 TEAE (aOR 1.22; 95%CI 0.16-9.53; p=0.9).
**Conclusion:** There was no significant difference in baseline CD4 comparing PWH and HIV- participants. Half of HIV- participants had CD4<350 cells/μL. The association between baseline CD4 and proportion of TEAE did not differ by HIV status. Overall, ICI did not appear to increase the risk of TEAE in PWH compared to HIV- participants, further supporting the safety of ICI for PWH with advanced cancer.

**Participant characteristics***

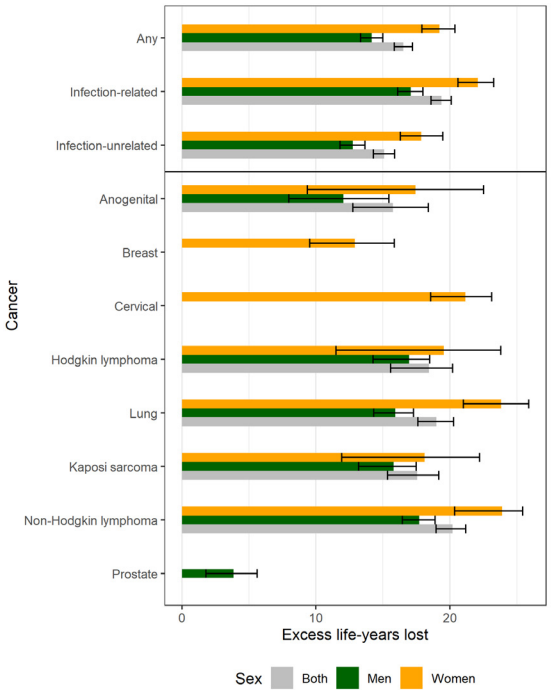
| | | HIV+ N=46 | HIV- N=56 | Unadjusted p-value |
|---|---|---|---|---|
| CD4 cells/uL | | 284.5 (187.0, 495.0) | 356.0 (260.0, 470.0) | 0.22 |
| CD4 count categories | <350 | 27 (59%) | 23 (50%) | 0.4 |
| | >=350 | 19 (41%) | 23 (50%) | |
| CD4+ (cells/uL) | <200 | 13 (28%) | 7 (15%) | 0.31 |
| | 200-350 | 14 (30%) | 16 (35%) | |
| | >350 | 19 (41%) | 23 (50%) | |
| Cancer type | Other | 13 (28%) | 0 (0%) | <0.001 |
| | Virus-associated | 33 (72%) | 56 (100%) | |
| HPV-associated | Non-HPV | 38 (83%) | 0 (0%) | 0.001 |
| | HPV-associated | 8 (17%) | 56 (100%) | |
| Age | | 54.0 (47.0, 61.0) | 58.0 (48.0, 64.6) | 0.5 |
| Sex | Male | 42 (91%) | 20 (36%) | <0.001 |
| | Female | 4 (9%) | 36 (64%) | |
| Race | Black | 17 (40%) | 0 (0%) | <0.001 |
| | White | 24 (57%) | 46 (92%) | |
| | Native Hawaiian or other Pacific Islander | 1 (2%) | 0 (0%) | |
| | Asian | 0 (0%) | 2 (4%) | |
| | Multiracial | 0 (0%) | 2 (4%) | |
| Ethnic group | Hispanic or Latino | 5 (11%) | 6 (11%) | 0.9 |
| | Not Hispanic or Latino | 40 (87%) | 48 (86%) | |
| | Not Reported | 1 (2%) | 2 (4%) | |
| Absolute neutrophil count, X1000/uL | | 3.4 (2.5, 4.6) | 4.0 (3.0, 5.3) | 0.02 |
| Absolute lymphocyte count, X1000/uL | | 1.4 (1.0, 1.9) | 0.9 (0.6, 1.4) | 0.01 |

* Data are presented as n (%) or *median (inter-quartile-range, IQR)
** Two-sample Wilcoxon rank-sum (Mann-Whitney) test

## 557 EXCESS MORTALITY ASSOCIATED WITH CANCER IN A PRIVATE HIV CARE PROGRAM IN SOUTH AFRICA

**Yann Ruffieux**[1], Hannes Mouton[2], Andreas D. Haas[1], Matthias Egger[1], Gary Maartens[3], Eliane Rohner[1]
*[1]Institute of Social and Preventive Medicine, Bern, Switzerland, [2]Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa, [3]University of Cape Town, Cape Town, South Africa*

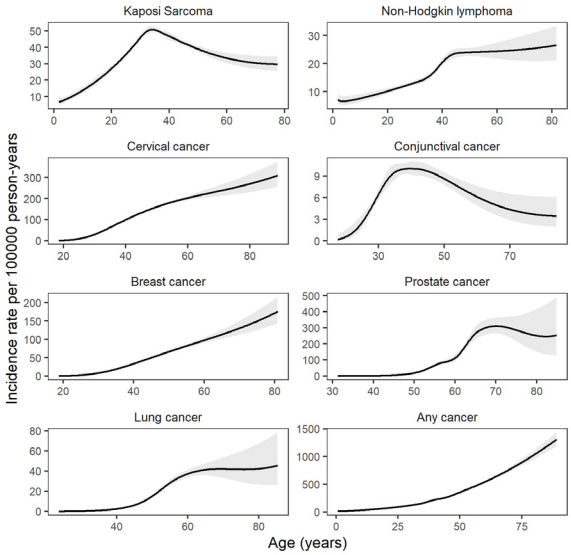
**Background:** Data on mortality in people living with HIV (PLWH) and cancer in South Africa are scarce. We quantified excess mortality associated with different cancer types in a private South African HIV disease management program.
**Methods:** We analyzed routine data from the Aid for AIDS (AfA) disease management program, covering the years 2012-2018. Information on mortality was ascertained through a linkage with mortality surveillance data from the South African National Population Register. We followed PLWH aged ≥18 years from their date of program enrolment until transfer out, death, or database closure. Cancer diagnoses were based on ICD-10 codes (C00-C99) from hospital reimbursement claims. We estimated the excess life-years lost (ELYL) associated with cancer by comparing the remaining life expectancy before the age of 75 in PLWH diagnosed with cancer to that in PLWH without cancer. We computed ELYL for the most common infection-related (anogenital and cervical cancers, Hodgkin lymphoma, Kaposi sarcoma, non-Hodgkin lymphoma) and infection-unrelated cancer types (breast, lung, prostate).
**Results:** Of 122,051 included PLWH, 2,675 were diagnosed with cancer, with a median age at diagnosis of 45 years (interquartile range 38-53). The mortality rate was 12/100 person-years (py) (95% confidence interval [CI] 11-13) in PLWH with cancer and 0.8/100 py (95% CI 0.7-0.9) in those without cancer. Among the common cancers, the highest mortality rate was observed in PLWH with lung cancer (39/100 py, 95% CI 30-48), non-Hodgkin lymphoma (19/100 py, 95% CI 16-22), and cervical cancer (14/100 woman-years, 95%CI 11-18). A person with cancer was estimated to lose 16.5 years of life (95% CI 15.9-17.2) compared to a person without cancer (Figure) with women losing more years (19.2 ELYL, 95% CI 17.9-20.4) than men (14.2 ELYL, 95% CI 13.3-15.0). Infection-related cancers were associated with higher ELYL (19.4, 95% CI 18.6-20.1) than infection-unrelated cancers (14.5, 95% CI 14.3-15.9). Among the common cancer types, non-Hodgkin lymphoma yielded the highest ELYL (20.2, 95% CI 19.0-21.2), followed by lung cancer (19.0, 95% CI 17.6-20.3), cervical cancer (18.7, 95% CI 16.2-20.7), Hodgkin lymphoma (18.4, 95% CI 15.6-20.2), and Kaposi sarcoma (17.6, 95% CI 15.4-19.2).
**Conclusion: In** South Africa, cancer often affects PLWH in their middle age and leads to many ELYL. Cancer prevention efforts are essential to improve life expectancy for PLWH.




## 558 AGE AND CANCER INCIDENCE IN 5.2 MILLION PEOPLE LIVING WITH HIV IN SOUTH AFRICA

**Yann Ruffieux**[1], Mazvita Muchengeti[2], Victor Olago[2], Tafadzwa G. Dhokotera[3], Julia Bohlius[3], Matthias Egger[1], Elvira Singh[2], Eliane Rohner[1]
*[1]Institute of Social and Preventive Medicine, Bern, Switzerland, [2]National Health Laboratory Service, Johannesburg, South Africa, [3]Swiss Tropical and Public Health Institute, Basel, Switzerland*

**Background:** Cancer incidence generally increases with older age, but this is not necessarily true for all cancer types. We examined incidence rates of various cancers as a function of age in people living with HIV (PLWH) in South Africa.
**Methods:** The South African HIV Cancer Match (SAM) Study is a nationwide cohort of PLWH in South Africa, based on a linkage between HIV-related laboratory records from the National Health Laboratory Service and cancer diagnoses from the National Cancer Registry for the period 2004-2014. PLWH who had ≥2 HIV-related tests on separate days were included. PLWH were considered at risk from the time of their first HIV-related test to database closure or 6 months after their last HIV-related test, whichever came first. We modelled incidence rates per 100,000 person-years (py) as a function of age for the most common cancer types using natural splines.
**Results:** Of 5,222,827 PLWH, 29,580 developed cancer for an overall incidence rate of 192/100,000 py. The most common cancers were cervical cancer (n=7,418; 67/100,000 woman-years), Kaposi sarcoma (n=6,380; 41/100,000 py), breast cancer (n=2,707; 25/100,000 woman-years), non-Hodgkin lymphoma (n=2,590; 16.7/100,000 py), conjunctival cancer (n=1,080, 7/100,000 py), lung cancer (n=734; 5/100,000 py), and prostate cancer (n=652; 15/100,000 man-years). Cancer rates varied by age (Figure). The incidence rate per 100,000 py for any cancer increased from 68 (95% CI 65-71) at age 20 to 222 (95% CI 216-228) at age 40, and 541 (95% CI 528-555) at age 60. For Kaposi sarcoma and conjunctival cancer, the incidence rates peaked at age 34 (54/100,000 py; 95% CI 49-53) and age 40 (10/100,000 py; 95% CI 9-11), respectively. The rate of non-Hodgkin lymphoma per 100,000 py increased from 10 (95% CI 9-11) at age 20 to 24 (95% CI 22-25) at age 45. The prostate cancer rate per 100,000 man-years increased from 18 (95% CI 16-22) at age 50 to 311 (95% CI 266-363) at age 70. The lung cancer rate per 100,000 py increased from 3 (95% CI 2-3) at age 40 to 37 (95% CI 34-41) at age 60. The cervical and breast cancer rates increased steadily with age.
**Conclusion:** The rates of most cancers increased with age. However, Kaposi sarcoma and conjunctival cancer rates peaked in middle-aged PLWH. These peaks may be due to complex interactions between age and immunodeficiency, duration of HIV infection, access to antiretroviral therapy, or exposure to underlying causes, for example human herpesvirus 8 or ultraviolet light.

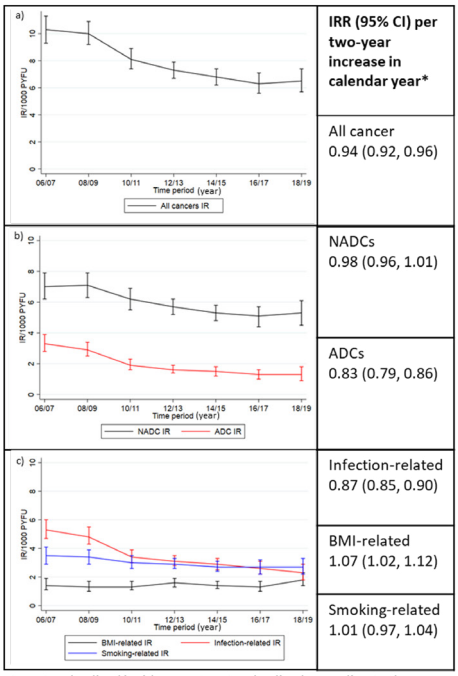



## 559 TRENDS IN CANCER INCIDENCE IN DIFFERENT MODERN ART ERAS AMONG PEOPLE LIVING WITH HIV

Lauren **Greenberg**[1]
*[1]University College London, London, UK*

**Background:** Cancer is one of the leading causes of death amongst people living with HIV (PLWH). There are limited international data assessing cancer trends across different contemporary antiretroviral therapy (ART) eras.
**Methods:** PLWH from the D:A:D and RESPOND cohort collaborations were followed from baseline (in D:A:D defined as the latest of date of study entry and 1 Jan 2006; in RESPOND, the latest of local cohort enrolment and 1 Jan 2012) until earliest of first cancer event, final follow-up (FU), or 1 Feb 2016 in D:A:D or 31 Dec 2019 in RESPOND. Age-standardised cancer incidence rates (IRs) were calculated from 2006-2019. Poisson regression was used to assess temporal trends, adjusted for potential confounders.
**Results:** Overall, 66,636 individuals were included. Median baseline age was 41 years (interquartile range [IQR] 34-48), median CD4 count 455 cells/μL (IQR 295-647) and 74% were male; 46% were ART-experienced with viral load (VL) <200 copies/mL (vs 35% ART-naïve, 19% ART-experienced with VL ≥200 copies/mL) and 34% were current smokers (vs 13% previous smokers, 24% never smokers, 29% unknown). With median FU of 7.5 years (IQR 3.8-11.6), there were 3634 incident cancers during 489,856 person-years of FU (PYFU; IR 7.4/1000 PYFU [95% confidence interval (CI) 7.2-7.7]). Among 3634 cancers, 1078 were AIDS-defining cancers (ADCs) and 2556 non-ADCs (NADCs); 1775 were infection-related cancers (IRCs), 1273 smoking-related cancers (SRCs), and 608 BMI-related cancers (BRCs; groups were not mutually exclusive). Age-standardised IRs for overall cancer decreased over time; ADCs and IRCs decreased substantially whilst NADCs and SRCs remained fairly constant, and BRCs increased (Figure). After adjusting for a wide range of confounders including age, baseline CD4 count, viral load, prior cancer events, and current smoking status, the incidence of all cancer (IR ratio per 2-year increase in calendar period: 0.96 [95% CI 0.94-0.98]), ADCs (0.83 [0.79-0.86]), and IRCs (0.87 [0.85-0.90]) decreased over time, whilst NADCs (1.03 [1.00-1.06]), SRCs (1.05 [1.01-1.09]) and BRCs (1.10 [1.04-1.16]) increased.
**Conclusion:** In this large, international collaboration, the age-standardised incidence of all cancers, ADCs and IRCs decreased over time, while NADCs and SRCs remained constant, and BRCs increased. Results were fairly similar after adjusting for demographics, smoking, BMI, comorbidities, coinfections, and HIV and ART-related factors, suggesting more research is needed to understand the cancer trends observed.

**Figure - age-standardised incidence rates over time of: a) all cancer, b) AIDS and non-AIDS cancer, c) infection, smoking, and BMI-related cancer**




*Age-standardised incidence rates standardised according to the age distribution of the D:A:D and RESPOND population in 2015.*
**IRR estimated from a Poisson regression model, adjusted for age only.*
*Infection-related cancers: non-Hodgkin's lymphoma, Kaposi's sarcoma, Hodgkin's lymphoma, anal, liver, cervical, stomach, penile, oropharyngeal; Smoking-related cancers: lung, liver, head and neck, cervical, bladder, colon, pancreatic, kidney, rectum, oesophageal, stomach, acute myeloid leukaemia; BMI-related cancers: liver, breast, colon, kidney, pancreatic, rectum, oesophageal, gall bladder, thyroid.*

## 560 THE SOUTH AFRICAN HIV CANCER MATCH STUDY: COHORT PROFILE

**Mazvita Muchengeti**[1], Victor Olago[1], Matthias Egger[2], Tafadzwa G. Dhokotera[3], Elvira Singh[1], Julia Bohlius[3]
*[1]National Health Laboratory Service, Johannesburg, South Africa, [2]Institute of Social and Preventive Medicine, Bern, Switzerland, [3]Swiss Tropical and Public Health Institute, Basel, Switzerland*

**Background:** South Africa has the largest population of people living with HIV in the world. However, there is limited data on HIV-related cancers in sub-Saharan Africa, where two-thirds of the world's HIV-infected population live. We aimed to create a national cohort of people living with HIV (PLWH) and cancer outcomes in South Africa to assess the spectrum and risk of cancer in PLWH in the context of the evolving South African HIV epidemic.
**Methods:** We retrieved laboratory records from PLWH (both children and adults) who accessed HIV care in public sector facilities in South Africa from 2004 – 2014. We used privacy preserving record linkage methods to deduplicate HIV records from the National Health Laboratory Service and to link cancer records from the National Cancer Registry (doi:10.31730/osf.io/wzxbv). We assessed the linkage quality by deriving precision (P), recall (R) and the F measure. We included all PLWH with ≥2 HIV laboratory records in the cohort and estimated cancer incidence rates (IR) per 100,000 person-years (pys) for the five most common cancers. We measured pys from the first laboratory test until incident cancer diagnosis (if any) or the last HIV-related laboratory record plus a grace period of 180 days. We defined incident cancer cases as cancers diagnosed after the first HIV-related laboratory record and before the end of the grace period.
**Results:** We retrieved 52.8 million HIV-related laboratory records and 664,869 cancer records. Deduplication resulted in 13.1 million unique PLWH; of these we included 5.2 million PLWH in the cohort. For the linkages between cancer and HIV records, P was 0.98, R was 0.96 and F 0.97. At cohort entry, median age was 33.0 years (interquartile range [IQR]: 26.2 - 40.9), whilst the median age at cancer diagnosis in records linked to an HIV record was 45.9 years; (IQR: 36.8 – 55.1). The median CD4 cell count 290 was cells/μL (IQR: 153 – 465); 69% were female. The most common cancers were cervical cancer (IR 66/100,000 pys), Kaposi sarcoma (IR 40/100,000 pys), breast cancer (IR 17/100,000 pys), non-Hodgkin lymphoma (16/100,000 pys) and eye cancer (8/100,000 pys).
**Conclusion:** The South African HIV Cancer Match Study is a unique resource for research and surveillance of malignancies in PLWH in the context of the evolving South African HIV epidemic. Regular updates of the cohort and inclusion of additional laboratory information are being planned and underway.

**Table 1: Top ten cancers stratified by sex**

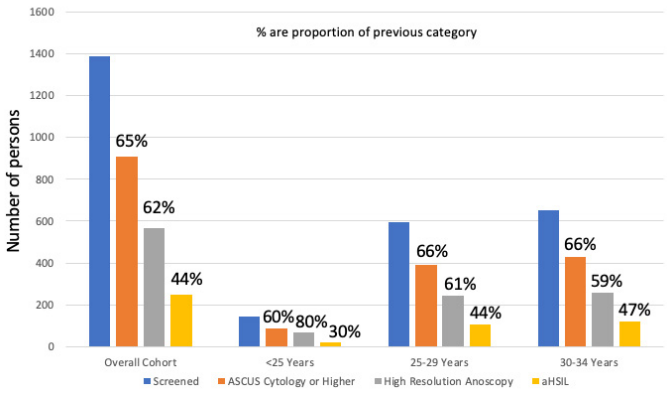
| | Incident cancer cases | | | Cancer incidence rate per 100 000 person-years (95% CI)* | | |
|---|---|---|---|---|---|---|
| **Cancer type** | **Males** | **Females** | **Total** | **Males** | **Females** | **Total** |
| Cervical cancer | - | 7,433 | 7,433 | - | 66.0 (64.5 - 67.5) | - |
| Kaposi Sarcoma | 3,268 | 3,105 | 6,373 | 72.7 (70.2 - 75.2) | 27.6 (26.6 - 28.5) | 40.4 (39.4 - 41.4) |
| Breast cancer | 39 | 2706 | 2,745 | 0.9 (0.6 - 1.2) | 24.0 (23.1 - 24.9) | 17.4 (16.8 - 18.1) |
| Non Hodgkin lymphoma | 1,202 | 1,386 | 2,588 | 26.7 (25.2 - 28.2) | 12.3 (11.7 - 13.0) | 16.4 (15.8 - 17.0) |
| Eye cancer | 470 | 854 | 1,324 | 10.4 (9.5 - 11.4) | 7.6 (7.1 - 8.1) | 8.4 (7.9 - 8.9) |
| BCC | 647 | 450 | 1,097 | 14.4 (13.3 - 15.5) | 4.0 (3.6 - 4.4) | 7.0 (6.5 - 7.4) |
| SCC of skin | 454 | 432 | 886 | 10.1 (9.2 - 11.1) | 3.8 (3.5 - 4.2) | 5.6 (5.2 - 6.0) |
| Lung | 526 | 206 | 732 | 11.7 (10.7 - 12.7) | 1.8 (1.6 - 2.1) | 4.6 (4.3 - 5.0) |
| Prostate cancer | 660 | - | 660 | 14.7 (13.6 - 15.8) | - | - |
| Colorectal cancer | 291 | 363 | 654 | 6.5 (5.7 - 7.2) | 3.2 (2.9 - 3.6) | 4.1 (3.8 - 4.5) |
| **Total**** | **10,542** | **20,570** | **31,112** | **235.0 (230.5 - 239.5)** | **183.1 (180.6 - 185.6)** | **197.8 (195.6 - 200.0)** |
| Total excluding BCC and SCC of skin | 9,605 | 19,797 | 29,402 | 214.0 (209.8 - 218.3) | 176.2 (173.8 - 178.7) | 186.9 (184.8 - 189.1) |

## 561 PREVALENCE AND SEVERITY OF HPV-ASSOCIATED ANAL DISEASE IN PWH YOUNGER THAN 35

**Keith Sigel**[1], Michael M. Gaisa[1], Yuxin Liu[1]
*[1]Icahn School of Medicine at Mt Sinai, New York, NY, USA*

**Background:** Anal cancer is a major source of cancer morbidity for people living with HIV (PWH). Evolving guidelines recommend initiating anal cancer screening for PWH at age 35. With emerging evidence supporting the cancer prevention benefits of anal high-grade squamous intraepithelial lesion (HSIL) treatment, we sought to analyze outcomes of anal dysplasia screening for PWH < 35 years.
**Methods:** Between January 2014 and August 2020, we identified initial anal cytology and high-risk HPV (hrHPV) test results for all PWH < 35 years who underwent screening in our health system. We then collected information on subsequent high-resolution anoscopy (HRA)-guided biopsies and linked cancer registry entries (to identify any anal cancer diagnoses) for this cohort. Using these data we compared screening and HRA outcomes according to demographics, CD4 count, HPV vaccination status and age subgroups.
**Results:** 1,389 PWH < 35 underwent anal dysplasia screening during the study period. Most (>90%) were 25-34 years of age and the vast majority were men (93%) of whom 98% were men who have sex with men. Only 28% received at least one dose of HPV vaccine before their initial screening cytology. Most subjects (66%) had cytologic abnormalities of ASCUS or greater (11% had HSIL cytology). 75% of cytology samples were co-tested for hrHPV with 85% of tests positive for any hrHPV type and 43% positive for HPV 16 and/or 18. Of subjects with abnormal screening cytology 62% underwent subsequent HRA which yielded anal HSIL in 44%. Among PWH who underwent HRA women had substantially less histologic HSIL than men (18% versus 42%; p=0.002). There was no significant difference in the proportion of persons diagnosed with histologic HSIL by age subgroup (<25, 25-29, 30-34; p=0.7). CD4 count at initial screen was not associated with severity of cytologic abnormalities, hrHPV infection or HSIL diagnosis. History of HPV vaccination was associated with lower rates of HPV 16/18 infection (38% in vaccinated versus 45% in unvaccinated, p=0.02) but did not impact rates of overall hrHPV infections or eventual HSIL diagnoses. No incident cancers were diagnosed during the follow-up period.
**Conclusion:** High-risk HPV infection, cytologic abnormalities, and associated histologic HSIL were all common in PWH under age 35. With emerging evidence regarding the benefits of anal HSIL treatment, the role of screening should be further investigated in this population.

Figure. Anal precancer screening cascade for PWH younger than 35.




## 562 FACTORS ASSOCIATED WITH ANAL DYSPLASIA AMONG YOUNG MSM AND TW WITH HIV IN ATLANTA

**Leah Loerinc**[1], Amy Scheel[1], Amelia Thompson[2], Kristin Wall[1], Scott Gillespie[1], Molly McCallum[3], Lisa Flowers[1], Andres Camacho-Gonzalez[1]
*[1]Emory University, Atlanta, GA, USA, [2]AdventHealth for Children, Orlando, FL, USA, [3]University of Colorado, Aurora, CO, USA*

**Background:** Men who have sex with men (MSM) and transgender women (TW) with HIV are disproportionately affected by anogenital human papillomavirus (HPV) infection with high rates of anal intraepithelial neoplasia (AIN) and subsequent anal cancer. However, there are no national guidelines for anal cancer screening and vaccination rates among men and TW remain low. There is a need to understand risk factors for high-grade anal dysplasia to inform screening guidelines and preventative measures in these groups. In this study, we evaluated factors associated with high-grade anal dysplasia on anal biopsy among young MSM and TW with HIV in Atlanta, GA.

**Methods:** Retrospective chart review was conducted for all cisgender MSM and TW with HIV aged 13-25 at the Grady Ponce and Family Youth Clinic in Atlanta, GA from 2009-2020. Participants who underwent anal biopsy over the study period were included. Data were collected on patient characteristics, sexual history, and anal histology results, with high-grade anal dysplasia defined as AIN 2 or 3. Associations between clinical and demographic factors with high-grade anal dysplasia were estimated using logistic regression (SAS v9.4, Cary, NC). Adjusted odds ratios (aORs) and 90% confidence intervals (CIs) are reported. Statistical significance was assessed at the 0.10 alpha-level.

**Results:** 103 MSM and TW with HIV were included. The mean age was 19.7 (SD: ±1.9) years. 91% were Black and 98% were horizontally infected with HIV. 63% of participants had high-grade anal dysplasia on anal biopsy. Having ever received surgical treatment for anogenital HPV (aOR 2.59, 90%CI 1.18-5.66, p=0.05) and being incompletely or unvaccinated against HPV (0-2 doses) relative to being fully vaccinated (3 doses) (aOR 5.34, 90%CI 1.30-21.93, p=0.05) were strongly associated with high-grade anal dysplasia, controlling for age and CD4 T-cell count at time of biopsy.

**Conclusion:** Our study found disproportionately high rates of high-grade anal dysplasia on anal biopsy among young MSM and TW with HIV. Furthermore, those who had ever received surgical treatment for anogenital HPV and those who were incompletely or unvaccinated against HPV were more likely to have high-grade disease. To our knowledge, this is the first study to show an association between vaccination status and high-grade anal dysplasia in this population. Our data emphasize the urgent need to improve HPV vaccination efforts and to pursue larger surveillance studies of high-grade disease among young MSM and TW with HIV.

**Table:** Factors associated with high-grade anal dysplasia on anal biopsy, N=103 MSM and TW

| | aOR | 90%CI | | p-value |
|---|---|---|---|---|
| Age (per year increase) | 1.22 | 0.98 | 1.53 | 0.14 |
| CD4 count at time of biopsy (per cells/μL increase) | 1.00 | 0.99 | 1.00 | 0.73 |
| Vaccination status (incomplete vs. complete) | 5.34 | 1.30 | 21.93 | 0.05 |
| Surgical treatment for anogenital HPV ever (yes vs. no) | 2.59 | 1.18 | 5.66 | 0.05 |

aOR: adjusted odds ratio, CI: confidence interval, HPV: human papilloma virus; MSM: men who have sex with men, TW: transgender women

## 563 GENITAL AND ANAL CYTOLOGY: HPV COTESTING RESULTS FROM 381 WOMEN LIVING WITH HIV

**Michael M. Gaisa**[1], Kevin Weiss[1], Keith Sigel[1], Yuxin Liu[1]
*[1]Icahn School of Medicine at Mt Sinai, New York, NY, USA*

**Background:** Women living with human immunodeficiency virus (WLH) are at increased risk for high-risk human papillomavirus (HR-HPV)-associated cervical and anal cancer. While cervical cancer screening has been the standard of care, anal cancer screening has not yet been universally adopted. Comparative data on cervical and anal HR-HPV positivity and cytological abnormalities are sparse among WLH in the era of antiretroviral therapy.

**Methods:** Between 2012-2019, we identified WLH with available data on initial anal cytology screening/HR-HPV genotyping and corresponding cervical/vaginal co-testing within 6 months. Univariable analyses were performed for risk factors of anal HPV infection. Clinical prediction nomograms were developed to calculate the probability of anal HR-HPV infection, HPV 16/18 infection, and cytological abnormalities of ASCUS or worse based on cervical screening results and clinical HIV parameters.

**Results:** 381 WLH met inclusion criteria. The median age was 49 years (range: 20-81); most were non-Hispanic Blacks (56%) and active smokers (63%). Median time since HIV diagnosis was 16 years (interquartile range: 9-23). Cytological abnormalities were more prevalent in anus (44%) than cervix (22%) with low/moderate concordance between the two sites. HR-HPV was detected in 65% of participants at any of the screened anatomic sites: 35% at anus only, 4% at cervix only and 26% at both sites. HPV16/18 was detected in 27% of participants: 19% at anus only, 2% at cervix only and 6% at both sites. Univariable analyses indicated that anal HR-HPV was significantly associated with cervical/vaginal HR-HPV infection, current CD4 T-cell count ≤ 500 cells/mm$^3$, HIV RNA viral load > 50 copies/ml, and nadir CD4 T-cell count < 200 cells/mm$^3$ (p<0.001). Factors not significantly associated with anal HR-HPV included age, race, smoking, and the length of HIV infection. A nomogram predicting anal HR-HPV infection based on nadir CD4 T-cell count < 200 cells/mm$^3$, cervical/vaginal cytology ≥ASCUS and cervical/vaginal HR-HPV positivity yielded prediction probabilities ranging from 39% (all predictors absent) to 93% (all predictors present).

**Conclusion:** High prevalence of anal HR-HPV infection and cytological abnormalities among WLH underscore the importance of anal cancer screening independent of preceding or concurrent genital disease. Clinical data can help stratify the risk of anal disease via prediction nomograms, although further prospective validation is warranted.

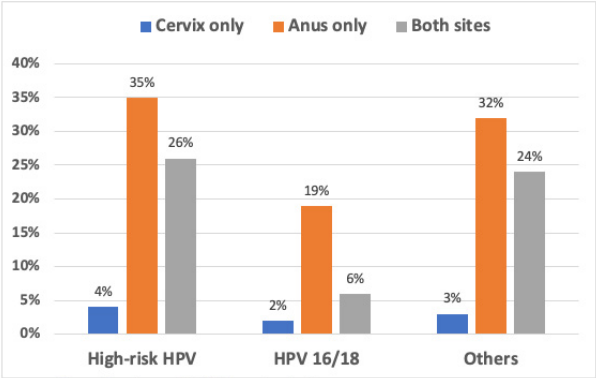



**Figure.** Prevalence of hrHPV by anatomic site.

## 564 EVALUATING HPV TESTING FOR CERVICAL CANCER SCREENING IN FOUR COUNTRY'S HIV PROGRAMS

**Jessica Joseph**[1], Owen Demke[1], Lola Ameyan[2], Joseph Bitilinyu-Bango[3], Jibrin Kama[2], Marvin Lubega[4], Bernard Madzima[5], Tasimba Mhizha[6], Andrew Musoke[4], Timothy Tchereni[7], Shaukat Khan[1]
*[1]Clinton Health Access Initiative, Boston, MA, USA, [2]Clinton Health Access Initiative, Abuja, Nigeria, [3]Ministry of Health, Lilongwe, Malawi, [4]Clinton Health Access Initiative, Kampala, Uganda, [5]Ministry of Health and Child Care, Harare, Zimbabwe, [6]Clinton Health Access Initiative, Harare, Zimbabwe, [7]Clinton Health Access Initiative, Lilongwe, Malawi*

**Background:** Cervical cancer disproportionately affects women in resource-limited settings, as access to secondary prevention is currently limited. Women living with HIV (WLHIV) are at increased risk of human papillomavirus

(HPV) infection and once infected are at greater risk of progression to cancer; therefore, timely screening and treatment is of utmost concern. The goal of the pilots was to introduce integrated HPV testing using existing NAT platforms in public health HIV programs in sub-Saharan Africa and describe the cascade of care.

**Methods:** Observational, prospective pilot studies were conducted across 32 facilities in Malawi, Nigeria, Uganda, and Zimbabwe between September 2019 and April 2021. All countries except Zimbabwe utilized near-point-of-care (POC) devices for HPV testing. Zimbabwe conducted testing on platforms at a centralized laboratory; Uganda conducted HPV testing on both near-POC and centralized platforms. Self-collected sampling was offered as an alternative to clinician-sampling in Malawi, Nigeria, and Uganda. The target population was WLHIV; age-inclusion criteria followed country guidelines, ranging from 25-49 years. All women identified as HPV-positive were to receive visual inspection with acetic acid (VIA), and if pre-cancerous or cancerous lesions were evident, receive treatment or referral.

**Results:** Across the four countries, 14155 tests were conducted, with 4% of tests invalid and 5% missing results, leaving 12962 valid results (Table). HPV prevalence was 35%. 66% of HPV-positive women received their result (median time to result: 34 days, interquartile range: 7-64). Among women who received VIA, 584 (22%) were VIA-positive and among those 86% received treatment (70% on same-day as VIA). 30 (1%) were suspected of cancer and of those 80% had a documented referral for tertiary care. In Uganda, 53% of HPV-positive women tested at centralized laboratory received VIA versus 73% of women tested on near-POC devices (p=0.07).

**Conclusion:** HPV testing was found to be feasible across the four pilot countries in a public health setting. While many women did not receive their HPV results, these pilots were conducted during COVID-19, where lockdowns and other disruptions to health-seeking behavior were major barriers. Once women did receive VIA, most who required treatment received it, the majority on the same day. With proper systems in place, use of HPV testing for cervical cancer screening program as recommended by WHO is a promising model in low- and middle-income countries.

Table: HPV testing and treatment cascade among women living with HIV

| | Malawi n(%) | Nigeria n(%) | Uganda n(%) | Zimbabwe n(%) | All n(%) |
|---|---|---|---|---|---|
| Total Tested | 2320 | 1351 | 6611 | 3,873 | 14155 |
| Self-collected sample | 598 (26%) | 797 (59%) | 6611 (100%) | 0 (0%) | 1395 (10%) |
| near-POC device | 2320 (100%) | 1351 (100%) | 4551 (69%) | 0 (0%) | 8222 (58%) |
| Hub | 1939 (84%) | 0 (0%) | 4551 (69%) | NA | 6490 (46%) |
| Valid Result | 2203 (95%) | 1177 (87%) | 6012 (91%) | 3570 (92%) | 12962 (92%) |
| HPV-positive | 957 (43%) | 302 (26%) | 1827 (30%) | 1425 (40%) | 4511 (35%) |
| Patient Received Result | 529 (55%) | 261 (86%) | 1279 (70%) | 220 (61%) | 2289 (66%) |
| Patient Received VIA | 443 (84%) | 210 (80%) | 823 (64%) | 1223* | 2699* |
| VIA-positive | 81 (18%) | 104 (50%) | 167 (20%) | 232 (19%) | 584 (22%) |
| Received Treatment | 65 (80%) | 104 (100%) | 124 (74%) | 208 (90%) | 501 (86%) |
| VIA-suspected of cancer | 7 (2%) | 0 (0%) | 14 (2%) | 9 (1%) | 30 (1%) |
| Patient Referred | 4 (57%) | NA | 12 (86%) | 8 (89%) | 24 (80%) |

*In Zimbabwe, 1067 women received VIA that did not first receive their result; they are added back into the cascade here.

## 565 IMMUNOLOGICAL BIOMARKERS ASSOCIATED WITH ANAL DYSPLASIA IN PEOPLE LIVING WITH HIV

New Investigator Scholar

**Joaquin Burgos-Cibrian**[1], Cristina Mancebo Pérez[1], Nuria Massana[1], Antonio Astorga Gamaza[1], Stefania Landolfi[2], Vicenç Falcó[1], Maria José Buzón[1], Meritxell Genescà[1]

*[1]Vall d'Hebron Research Institute, Barcelona, Spain, [2]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain*

**Background:** Early detection of Squamous intraepithelial lesion (SIL) is essential to limit anal cancer development and progression. Accordingly, screening and treatment of these lesions in high-risk patients such as persons living with HIV (PLWH) is recommended. HIV-positive men who have sex with men (MSM) are at exceptionally high risk for SIL and therefore, understanding the local immunological mechanisms involved in the development and progression of this disease will be critical for prevention and novel treatment. Here, we aimed to determine the local immune microenvironment where high or low grade (H/L)-SIL develop.

**Methods:** A cross-sectional study with 47 men having sex with men (MSM) subjected to combination antiretroviral therapy (cART) was established. Screening for anal dysplasia included cytology, high-resolution anoscopy (HRA), HPV testing and histological examination. Multiple lymphocyte and myeloid immunological subsets were analyzed in a total of 54 anorectal biopsies by flow cytometry. Selected biomarkers were confirmed by immunohistochemistry.

**Results:** Age, nadir CD4 and time of viral suppression were associated with pathological samples and, in particular, with HSIL (pAge<0.005, pCD4nadir=0.003, pVSupression<0.05). Increased frequencies of T lymphocytes in the affected mucosa of HSIL group (p<0.02), indicating an infiltration or expansion of this subset was detected. Nevertheless, Resident Memory T cells expressing CD103 were less frequent in pathological biopsies (H/L-SIL), with a more pronounced effect on the CD4 subset (p=0.025). Increases in the frequency of Natural Killer (NK) expressing CD16 and overall NK activation measured by HLA-DR, were also associated with pathological samples (pNKCD16=0.015, pNKactv<0.02). As an indicator of inflammation, neutrophil infiltration defined as CD15+CD16+ cells, showed a gradual increase as the anorectal lesion progressed (p=0.012). This result was confirmed by immunohistochemistry.

**Conclusion:** Immunological tissue analyses revealed a complex immunological environment were the balance between resident effectors and inflammatory subsets was tilted towards the second in pathological samples. Neutrophil infiltration determined by CD15 staining may represent a valuable biomarker to determine dysplasia progression.

## 566 EXPRESSION OF IFN RECEPTORS IN ANAL CELLS FROM HIV-POSITIVE MEN DURING HPV INFECTION

New Investigator Scholar

**Mirko Scordio**[1], Federica Frasca[1], Giuseppe Oliveto[1], Leonardo Sorrentino[1], Agnese Viscido[1], Matteo Fracella[1], Letizia Santinelli[1], Eugenio Nelson Cavallari[1], Paolo Gozzo[1], Gabriella D'Ettorre[1], Guido Antonelli[1], Alessandra Pierangeli[1], Carolina Scagnolari[1]

*[1]Sapienza University of Rome, Rome, Italy*

**Background:** Persistent infections with high-risk (HR) HPVs are associated with anal cancer, with a particularly high risk in HIV+ individuals. To clarify the process that may lead to HPV persistence, we conducted a study on key genes of type I and III Interferon (IFN) pathways in HPV infected anal cells from HIV+ and HIV- men.

**Methods:** Anal canal brushing samples were prospectively collected from male patients attending a proctology clinic. Anal cells were divided into two aliquots: one for total DNA extraction and HPV detection, the second for RNA extraction and gene expression analysis. Detection of HPV DNA was performed by PCR and genotyping by sequencing. Transcripts of the genes coding for the type I IFNs Alpha2, Beta and Epsilon, of the subunits IFNAR1 and 2 of their receptor, of the type III IFNs lambda1 to 3, of their receptor specific subunit IL28R1, and the IFN-stimulated genes (ISG) MxA, ISG15, ISG56, IRF3, IRF7 were quantified by Real time PCR assays with relative quantification to the invariant gene GUS (the 2^−ΔCt method).

**Results:** Eighty Caucasian HIV+ men (mean age 46.6 years SD 9.6), on long-term ART, and 28 HIV- men (mean age 46.3 years DS 15.6) were enrolled in this study. HPV DNA was detected in 81.5% of the HIV+ men, and in 60.7% of the HIV- men (p=0.04). The most common genotypes were HPV 6 and HPV 16 in both groups; there was a comparable rate of HR-HPV (30.2% in the HIV+, 31.2% in the HIV-). No significant difference was observed in type I/III IFNs coding genes and for ISGs during LR or HR HPV infections in either HIV+ or HIV- men, with respect to the values detected in the HPV-negative groups. Differently, IFNAR1 and IFNAR2 were activated in HIV+ men in HPV infections, (KW test p=0.032 and p=0.033, respectively), with the highest levels in HR HPV infections, whereas in HIV- they were not. By contrast, IL28R1 was significantly downregulated in HIV+ individuals infected with LR HPVs and even more in the HR-HPV infected (KW test p=0.035), whereas IL28R1 did not vary in the HIV-.

**Conclusion:** Unlike what was reported in the cervical mucosa, in anal cells HPV seemed to poorly activate type I/III IFNs genes and related ISGs in HIV- and HIV+ men. Further studies in anal cells of patients in the early stages of infection and at follow-up, could help to clarify whether the dysregulated level of the IFN receptors in HPV/HIV coinfected patients may contribute to favor HPV persistence thus increasing the risk of anal cancer.

## 567 HPV DIFFERENTLY HIJACKS ANAL INTERFERON RESPONSE IN HIV-POSITIVE AND HIV-NEGATIVE MSM

**Eugenio Nelson Cavallari**[1], Letizia Santinelli[1], Mirko Scordio[1], Federica Frasca[1], Giuseppe P. Innocenti[1], Luca Maddaloni[1], Gabriella De Girolamo[1], Giancarlo Ceccarelli[1], Claudio M. Mastroianni[1], Alessandra Pierangeli[1], Carolina Scagnolari[1], Gabriella D'Ettorre[1]

*[1]Sapienza University of Rome, Rome, Italy*

**Background:** Human Papilloma virus (HPV) infection of the anal canal is common in men who have sex with men (MSM), though HIV+ MSM show higher rate of HPV persistence, HPV-related anal dysplasia (squamous intraepithelial

lesion, SIL) and anal cancer. Local interferon (IFN) response represents the first line of defense against HPV at the mucosal site. HPV has evolved multiple strategies to evade local IFN response, allowing for chronic infection, onset of anal SIL and, ultimately, anal cancer.
**Methods:** 70 HIV+ MSM and 30 HIV- MSM were enrolled. Individuals with detectable plasma HIV RNA (lower limit of detection 37 copies/ml) and/or diagnosis of anal cancer and/or inflammatory bowel disease were excluded. Participants underwent anal HPV test, anal cytology and high resolution anoscopy (HRA). Local interferon response was characterized trough the expression of a wide array of IFN related genes (IFNAR1, IFNAR2, INFβ, MxA, ISG15, ISG56, IRF1, IRF7, TLR3, TLR4, TLR8, TLR9, IFNλ1-3). Gene expression was evaluated trough Real Time RT-PCR performed on an additional anal brush.
**Results:** HIV+ and HIV- participants showed similar age (49.2 ± 5 and 48 ± 7; p=0.724). Anal HPV DNA tested positive in 72.2% of HIV+ and 47.6% of HIV- participants (p=0.008). Comparison of local IFN response between HIV+/HPV- and HIV-/HPV- participants showed higher expression of IFNAR1 (p=0.009), IFNβ (p=0.021), ISG15 (p=0.047), ISG56 (p=0.08), IRF7 (p=0.004), TLR3 (p=0.03), TLR4 (p=0.001) and TLR8 (p=0.08) in HIV+/HPV- subjects. Among HIV+ participants, HPV+ individuals showed a reduced expression of IFNAR1 (p=0.07), IFNβ (p=0.019), ISG15 (p=0.036), ISG56 (p=0.039), TLR3 (p=0.011), TLR4 (p=0.002), TLR8 (p=0.006), TLR9 (p=0.012), IFLλ2 (p=0.009) and IFNλ3 (p=0.038) in respect to HPV- subjects. Among HIV- participants, expression of IFN related genes was similar between HPV+ and HPV- individuals, with the only exception of IFNβ (p=0.053). Expression of IFN related genes was similar between HIV+/HPV+ participants with hr-HPV or low risk-HPV. The same was observed among HIV-/HPV+ participants. In both groups, HIV+/HPV+ and HIV-/HPV+, expression of IFN related genes was similar in the presence or absence of SIL.
**Conclusion:** In the absence of HPV infection, HIV+ MSM show higher anal IFN related genes expression in respect to HIV- MSM. HPV effectively hijacks anal IFN antiviral response in HIV+ MSM but not in HIV- MSM. Anal IFN related genes expression is not influenced by the presence of hr-HPV or anal SIL.

## 568 WHOLE-GENOME SEQUENCING OF KSHV REVEALS EVIDENCE FOR 2 AFRICAN LINEAGES

**Razia Moorad**[1], Angelica Juarez[1], Justin T. Landis[1], Linda J. Pluta[1], Megan V. Perkins[1], Avery Cheves[1], Dirk P. Dittmer[1]
*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** Kaposi sarcoma (KS)-associated herpesvirus (KSHV/ HHV-8) was first sequenced from the body cavity (BC) lymphoma cell line, BC-1, isolated from an AIDS patient in 1996. Few other KSHV genomes have been reported, since then. Our knowledge of sequence variation for this virus remains unclear. This study reports additional genomes from KS biopsies isolated in the USA and Africa, and demonstrates the evolutionary relationship of these recent genomes to those collected in the 1990s.
**Methods:** Sequencing libraries were manually prepared from 100ng total DNA using the Ion AmpliSeq Library Preparation Kit 2.0 and sequenced on the Ion Torrent S5 with default parameters. Bioinformatic analysis was performed on CLC Genomics Workbench v20.0.3. High quality, trimmed reads were mapped to the KSHV reference genome (NC_009333) with default parameters. Duplicate mapped reads were removed and variants were called. Consensus sequences were built based on quality score voting. Phylogenetic trees were built using the MAFFT alignment tool implemented in Geneious v9.1.8 with default parameters. The maximum likelihood trees using the General Time Reversible protein model with the gamma distribution for site variation, implemented in RAxML in Geneious v9.1.8, with 1000 bootstrap replicates, were built.
**Results:** More than 16 high coverage KSHV genomes, isolated from HIV positive KS patients in Sub-Saharan Africa and the USA were sequenced. A phylogenetic analysis of KSHV evolution based on the largest whole genome data set, yet, reveals the existence of an "African" lineage of KSHV, which represent the viruses that are responsible for 90% of the KS and KSHV-associated lymphoma burden in the world.
**Conclusion:** In conclusion our phylogenetic analysis indicates the existence of an 'African' lineage of KSHV. The recent KSHV isolates largely resemble those used as experimental tools (cell lines and bacmids); however, they also present with multiple mutations. It is unclear, which of these are associated with novel phenotypes.

## 569 IDENTIFICATION OF PROVIRAL INTEGRATIONS WITHIN HIV-ASSOCIATED B-CELL LYMPHOMAS

New Investigator Scholar

**Michael P. Rist**[1], Machika Kaku[1], Tyler Colson[1], Michael Freeman[1], John M. Coffin[1]
*[1]Tufts University, Boston, MA, USA*

**Background:** Defective HIV proviruses within a few specific genes have been associated with T cell clonal expansion and persistence during ART. Recently, proviruses integrated in STAT3 and LCK have been implicated in insertional mutagenesis driving rare cases of T cell lymphoma. However, B cell lymphomas are much more common HIV–associated cancers, and a case report by Katano et al. identified an HIV provirus within STAT3 in a B cell lymphoma in an individual with AIDS. HIV is not typically characterized as infecting B cells, but HIV positive individuals are at a great risk of developing non-Hodgkin's lymphomas of B cell origin despite being on ART. We hypothesize that site-specific HIV proviral integrations can lead to B cell transformation and may be a contributing cause to HIV-associated B cell lymphomas.
**Methods:** Whole genome amplified DNA samples extracted from formalin-fixed paraffin embedded HIV-associated B cell lymphoma samples were obtained from the AIDS and Cancer Specimen Resource and assessed for HIV provirus content by PCR targeting the U5 region of the LTR. Proviruses were quantified relative to CCR5, a human reference gene. Integration site analysis was performed on two DNA samples that showed significant quantities of HIV LTR per cell (Figure 1).
**Results:** Our screen identified 2 out 110 samples to be highly positive (between 0.3-5.0 copies/cell) for HIV proviruses, with many more containing significant, but lower, proviral DNA levels. The two highly positive samples were subjected to integration site analysis for detection characterization of the location of clonal proviruses. Both samples contained many uniquely detected integration sites. A clonal population was identified within at least one B cell lymphoma-associated gene, SGK1, but it comprised only a small percentage (1.2%) of total integration sites detected.
**Conclusion:** We have demonstrated the presence of high-levels of HIV provirus within a small fraction of HIV-associated B cell lymphoma. Although further studies will be required to confirm the precise cell type that contains them, B cells can be targets for HIV infection based on prior in vitro studies. HIV-driven B cell lymphoma may still be a possibility with detection of HIV integration within SGK1, a gene whose product associates with the STAT3 protein, found in a small percentage of one sample. Further work needs to be done to determine to what extent B cells become infected with HIV and to what extent its integration can lead to B cell lymphoma development.

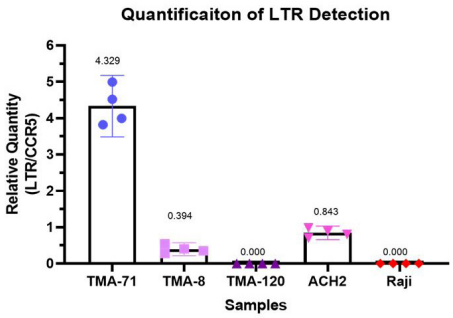


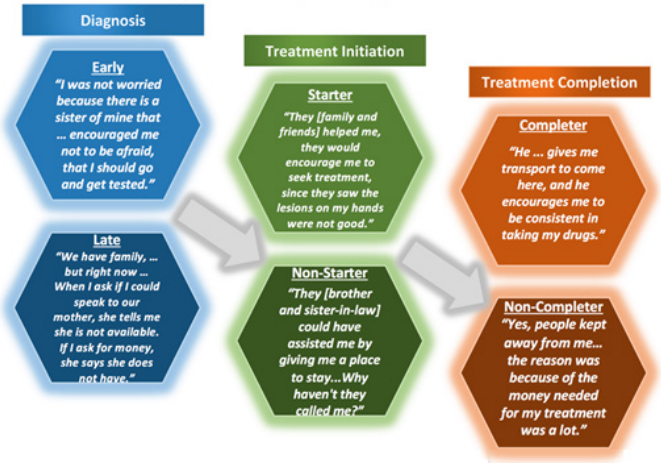

**Figure 1: Proviral Quantification of HIV B Cell Lymphoma Samples.** DNA samples were analyzed by qPCR for the presence of HIV U5 LTR and CCR5, human reference gene. Standard quantities of LTR and CCR5 were determined from an ACH2 standard curve. Relative quantities were determined by the ratio of LTR standard quantity to CCR5 standard quantity per sample.

## 570 ROLE OF SOCIAL SUPPORT IN DIAGNOSIS AND TREATMENT OF HIV-ASSOCIATED KAPOSI'S SARCOMA

**Rhea Singh**[1], Sigrid Collier[2], Aggrey Semeere[3], Helen Byakwaga[3], Miriam Laker-Oketta[3], Devon McMahon[1], Linda Chemtai[4], Merridy Grant[5], Lisa Butler[6], Ingrid V. Bassett[1], Samson Kiprono[7], Toby Maurer[8], Jeffrey N. Martin[9], Naftali Busakhala[7], Esther Freeman[1]
*[1]Massachusetts General Hospital, Boston, MA, USA, [2]University of Washington, Seattle, WA, USA, [3]Infectious Disease Institute, Kampala, Uganda, [4]Academic Model Providing Access to Healthcare, Eldoret, Kenya, [5]University of KwaZulu-Natal, Durban, South Africa, [6]University of Connecticut, Storrs, CT, USA, [7]Moi University, Eldoret, Kenya, [8]Indiana University, Indianapolis, IN, USA, [9]University of California San Francisco, San Francisco, CA, USA*

**Background:** Social support has been closely linked to health outcomes in both HIV and cancer. For people with HIV-associated malignancies in low resource settings, the process involved in diagnosis and treatment is particularly complex and time-consuming. In this context, social support may be an important contributor to timely diagnosis and treatment in Kaposi's Sarcoma (KS), one of the most common cancers in people living with HIV in Africa.
**Methods:** We nested a convergent mixed-methods study in a longitudinal cohort of people with HIV-associated KS in western Kenya. We measured social support every 16 weeks from February 2019 to December 2020 among all participants, using the 12-item Multidimensional Scale of Perceived Social Support (MSPSS) (score range: 12-84; higher score = more social support). We also conducted semi-structured interviews, using purposive sampling stratified by timing of diagnosis (delayed vs non-delayed) and chemotherapy status (not started, not completed, completed). We coded interviews using framework analysis based on sub-constructs in the MSPSS (family, friends, and significant others) and the following social support constructs (informative, instrumental, and emotional support).
**Results:** A total of 118 adults (61.1% male) with median age of 36.5 (IQR: 31.0, 42.0) completed the MSPSS questionnaires during at least one study visit. The median overall social support score across all timepoints was 84.0 (66.0, 84.0). Median subconstruct scores (4-items, score range: 4-28) were as follows: family (28.0; IQR: 27.0,28.0); friend (28.0; IQR:16.3,28.0); significant other (28.0; IQR:28.0,28.0). Social support scores increased significantly over time (adjusted $\beta = 0.11$, $p < 0.001$). In 88 semi-structured interviews, lack of social support was a major barrier to diagnosis and treatment in people with HIV-associated KS. Key themes among participants with late diagnosis or who did not start/complete treatment included lack of instrumental support (financial and physical assistance) as well as emotional support. Participants who completed chemotherapy commonly described larger support networks, access to instrumental support (financial support and assistance traveling to clinic visits) and having a friend or family member who was a healthcare worker.
**Conclusion:** Social networks are important sources of instrumental and emotional support in people with HIV-associated KS in western Kenya, and lack of social support may contribute to delays in the diagnosis and treatment of KS.

Figure 1: Qualitative Representation of Social Support in HIV-Associated Kaposi's Sarcoma: Experiences of Social Support contributing to KS diagnosis and treatment.




## 571 CHARACTERISTICS OF PATIENTS ADMITTED TO THE ICU WITH KSHV-ASSOCIATED DISEASES

**Megan E. Hansen**[1], Ralph Mangusan[1], Kathryn Lurain[1], Thomas Odeny[1], Jomy M. George[1], Crystal Lu[2], Maura Manion[3], Anaida Widell[1], Irene Ekwede[1], Denise Whitby[4], Thomas S. Uldrick[1], Robert Yarchoan[1], Ramya Ramaswami[1]
*[1]National Cancer Institute, Bethesda, MD, USA, [2]National Institutes of Health, Bethesda, MD, USA, [3]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [4]Frederick National Laboratory for Cancer Research, Frederick, MD, USA*

**Background:** Disorders caused by Kaposi sarcoma herpesvirus (KSHV) include Kaposi sarcoma (KS), primary effusion lymphoma (PEL), multicentric Castleman disease (MCD), and KSHV inflammatory cytokine syndrome (KICS). KSHV-associated disorders (KAD) can occur alone or concurrently among people with HIV (PWH) resulting in KSHV-associated inflammation (hypotension, elevated KSHV viral load (VL) and pancytopenia) that can lead to multiorgan dysfunction necessitating management in the intensive care unit (ICU). Little is known about the treatment and outcomes of patients (pts) with KAD in the ICU.
**Methods:** A retrospective review was conducted among pts with KAD who were admitted to the ICU at the NIH Clinical Center between 2010-2021. For the initial ICU admission, we studied KAD admission diagnoses, HIV and KSHV characteristics, and ICU interventions (including chemotherapy). The primary outcome was 60-day survival and median overall survival (OS) from ICU admission to death from any cause. Survival was evaluated using the Kaplan-Meier method and 2-sided log-rank tests to determine statistical differences between curves.
**Results:** 47 pts (44 cisgender male, 3 cisgender female) with KAD were admitted to the ICU with median age of 38 years. All but one pt had HIV co-infection. At ICU admission, 44 pts (94%) were on antiretroviral therapy (ART) with a median (med) CD4 count of 88 cells/μL (IQR 38.5 – 222.5) and med HIV VL of 23 copies/ml (IQR 20-95). Med KSHV VL was 885 copies/$10_6$ cells. Seven pts (3 with KS) had 1 KAD, 35 pts had 2 KAD (19 with KICS and KS), and 3 pts had 3 KAD (KS, MCD, and PEL) on ICU admission. Additionally, 2 pts had diffuse large B-cell lymphoma with KAD. The most common reason for ICU admission was respiratory failure (51%), followed by hypotension (34%), fever (26%), or a combination of these (49%). Ten (21%) pts (8 with KICS +/- KS) had a diagnosis of PEL and/or MCD made in the ICU following additional workup. Twenty-one (45%) pts received chemotherapy in the ICU for KAD and 16 (34%) of all pts required intubation. Survival at 60 days for all pts was 83% and median OS was 9 months following ICU admission. A diagnosis of PEL or KICS (+/- KS and/or MCD) at any time from ICU admission was associated with worse survival (P=0.01, Figure 1).
**Conclusion:** The majority of PWH and KAD admitted to the ICU were on ART, had well-controlled HIV, and presented with KSHV-associated inflammation. A diagnosis of KICS or PEL at any time from the ICU admission was associated with worse outcomes.

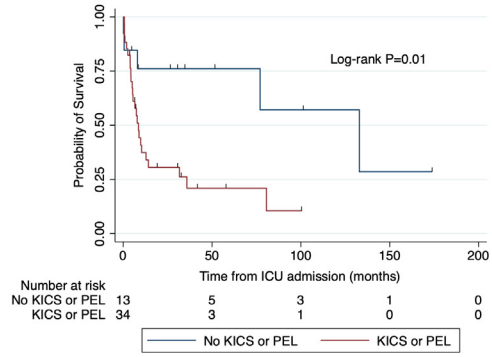



**Figure 1:** Kaplan-Meier curve demonstrating a diagnosis of KICS or PEL (+/- KS and/or MCD) at any time from ICU admission

## 572 POMALIDOMIDE INDUCES T-CELL ACTIVATION AND DECREASES SENESCENCE IN KAPOSI SARCOMA

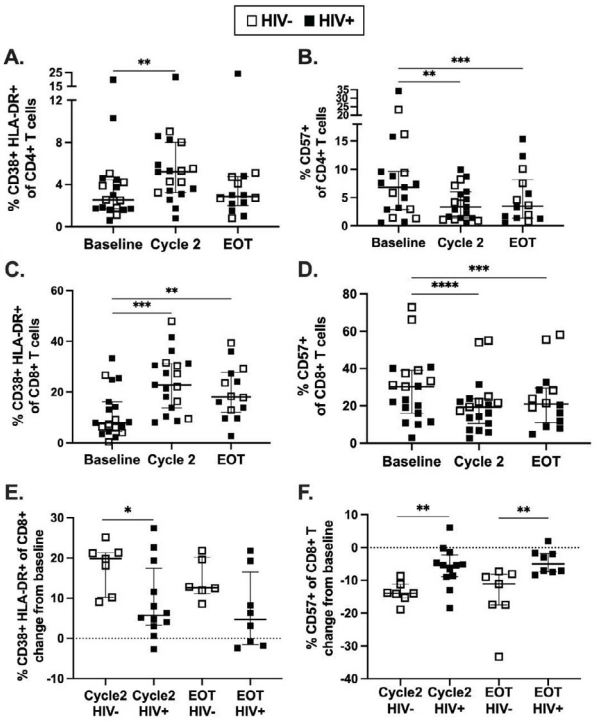
**Kathryn Lurain**[1], Mark Polizzotto[1], Laurie T. Krug[1], Kathleen M. Wyvill[1], Ramya Ramaswami[1], Robert Yarchoan[1], Thomas S. Uldrick[1], Irini Sereti[2]
*[1]National Cancer Institute, Bethesda, MD, USA, [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

**Background:** Kaposi sarcoma (KS) is an endothelial tumor strongly associated with HIV and CD4+ lymphocytopenia but may occur in those without HIV. Pomalidomide (Pom) is an immunomodulatory agent that can activate T cells and was recently approved by the US Food and Drug Administration for KS based on a Phase I/II study of participants (pts) with and without HIV conducted at the National Cancer Institute (NCT01495598). Differences in T cell phenotypes in those with and without HIV who develop KS is not well-studied. The in vivo effect of Pom on T cell function in people with KS is unknown.
**Methods:** We prospectively evaluated CD4+ and CD8+ T cell phenotypes in the first 19 of 28 pts with KS enrolled on the Pom study, 7 without HIV (median age=61 years) and 12 with HIV on ART (median age=48 years). Pts received Pom 5mg orally for 21 days of 28-day cycles for up to 1 year. Flow cytometry was performed on peripheral blood mononuclear cells at baseline (BL), after 2 cycles (C2), and at end-of-treatment (EOT). We evaluated BL differences by HIV status and the impact of Pom on lymphocyte counts and T cell subsets by Wilcoxon

signed-rank and Mann-Whitney tests. P<0.005 was considered significant and 0.005<p<="" div="">.

**Results:** At BL, HIV+ pts had lower CD4+ counts despite effective ART (median 416 vs 742 cells/uL, p=0.006), while HIV- pts had an increased proportion of CD57+ (senescent) CD8+ T cells (p=0.0072). There were no significant changes in total CD4+ and CD8+ at C2, although there was a strong trend towards increased CD8+ T cells at EOT (p=0.006), and there were significant decreases in CD19+ B cells at C2 and EOT (p=0.0003, p=0.0013). At C2, Pom led to an increased proportion of CD45RO+CD27+ (central memory) CD4+ (p=0.002) and CD8+ (p=0.0017) T cells. At C2, there was a decrease in CD45RO-CD27- (effector) CD4+ cells (p=0.0002) and expansion of CD38+/HLADR+ (activated) CD4+ (p=0.002) and CD8+ (p=<0.0001) T cells. Activation of CD8+ T cells persisted at EOT (p=0.0017). At C2 and EOT, there was reduction in the proportion of CD57+ CD4+ (p=0.0013, 0.0006) and CD8+ (p=<0.0001, 0.0004) T cells.

**Conclusion:** This analysis reveals that Pom in pts with KS decreases senescence while increasing activation of T cells. Our study also identifies baseline differences in T cell phenotypes in HIV+ and HIV- KS. Our observations provide important steps toward understanding the immune mechanisms of action of Pom in KS and may be relevant for other virus-associated cancers.




## 573 RISK AND PROTECTIVE FACTORS ASSOCIATED TO HTLV-1 MOTHER-TO-CHILD TRANSMISSION

**Gabriela S. Prates**[1], Arthur Paiva[2], Tatiane Assone[1], Rosa Marcusso[3], Jerusa V. Smith[3], Augusto Penalva[3], Jorge Casseb[1]

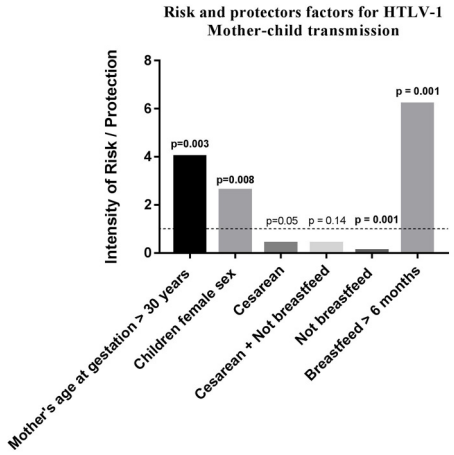
*[1]University of Sao Paulo, Sao Paulo, Brazil, [2]Hamad Healthcare Quality Institute, Doha, Qatar, [3]Institute of Infectology Emilio Ribas, Sao Paulo, Brazil*

**Background:** Maternal-to-child transmission of HTLV-1 (MTCT) may occur mainly through breastfeeding, but it is unclear whether other factors such as vaginal delivery, mother's age, baby's sex are important for this transmission. It has been ascribed to being breastfed for a long time (>6 months), high mother load and children of the same offspring are also important. The objective of this study was to determine the risk and protective factors for MTCT in a long term cohort in Sao Paulo, Brazil.

**Methods:** This was a retrospective study focused on women followed at the Instituto de Infectologia Emílio Ribas and their offspring. The test was offered to sexual partners, children, mothers and brothers, according to the diagnostic algorithm determined by the Ministry Health of Brazil. The MTCT was determined through the positive serology of the mother or siblings, and confirmed by Westblot and or Nested-PCR. Statistical analysis was performed on the software Graph Pad Prism 7.0 and the chi-square test was used for categorical variables.

**Results:** 292 positive mothers with an average age of 52.4 years were investigated so far. A total of 733 children were exposed to HTLV-1 during pregnancy. Up to now, 366 (49.9%) of offspring were tested, 85% (312/366) of them were negative for HTLV-1 and 15% (54/366) were HTLV-1 positive. Mother's age over 30 years at gestation (OR 4.0; 95% CI [1.9-8.0]; p value 0.003), the child being female (OR 2.6; 95% CI [1.5-4.8]; p value 0.008) and breastfeed for a period longer than 6 months (OR 6.2; 95% CI [2.8-13.4]; p value 0.0001) were risk factors for MTCT by HTLV-1. In contrast, cesarean delivery (OR 0.4; 95% CI [0.1-0.9]; p= 0.05) and not breastfeeding (OR 0.1; 95% CI [0.06-0.2]; p= 0.0001) are protective factors for MTCT (Figure 1).

**Conclusion:** Mother's age over 30 years at gestation increases the risk of HTLV-1 mother child transmission by 4 fold, the female child has 2.6 fold to be reached, and breastfeeding longer than 6 months increases 6.2 fold of risk for MTCT. Cesarean delivery offers 0.4 fold protection, but it was not statistically significant. More importantly, non-breastfeeding decreases MTCP by 0.1 fold. These findings may help to implement management measures for pregnant women with HTLV-1 infection could decrease the burden of this virus in endemic areas.




## 574 HTLV ADULT T-CELL LEUKEMIA/LYMPHOMA: A RETROSPECTIVE STUDY IN FRENCH GUIANA 2009-2019

**Karim Abdelmoumen**[1], Kinan D. Alsibai[2], Mathieu Nacher[3], Jean-Michel Cauvin[2], N'Detodji-Bill Wankpo[4], Pauline Naudion[4], Caroline Misslin-Tritsch[4], Felix Djossou[2], Antoine Gessain[5], Lionel Galicier[6], Olivier Hermine[7], Florin Santa[2], Pierre Couppie[2], Jean-Pierre Droz[2], Loïc Epelboin[2]

*[1]Université de la Réunion, Saint-Pierre, France, [2]Cayenne Hospital, Cayenne, French Guiana, [3]Université de Guyane, Cayenne, French Guiana, [4]Centre Hospitalier de l'Ouest Guyanais, Saint Laurent du Maroni, French Guiana, [5]Institut Pasteur, Paris, France, [6]Paris Center Hospital Group, Paris, France, [7]Necker Hospital, Paris, France*

**Background:** Adult T-cell leukemia / lymphoma (ATL) is one of the most aggressive cancers in the world. ATL occurs in 5% of the 10 million people living with HTLV-1 worldwide. French Guiana is a French overseas territory located in the Amazon region and one of the highest endemic areas of HTLV-1.

**Methods:** The objectives of the study were to describe the demographic, clinical and evolutionary characteristics of the population. We collected data from all patients diagnosed between 2009 and 2019. Patients were classified according to Shimoyama's classification. Continuous variables were compared using a Mann Whitney test. Survival curves were evaluated by the Kaplan-Meier method. The assessment of prognostic factors was based on a Cox proportional hazards model.

**Results:** Over the 11 years study period, 41 patients were identified, among whom 56% were women, with a median age of 54 years at diagnosis (IQR 42- 64; range 17-88). Sixteen (39%) patients were Maroons, a cultural group descendant of the African slaves of former Dutch Guiana. Among the study population, 23 (56%) had an acute-type, 14 (34%) a lymphoma-type, 1 patient had a chronic form and 1 patient had a primary cutaneous tumour. Hypercalcemia was associated with the acute-type (69.5% in the acute group vs. 42.8% in the lymphoma group; p = 0.015). The first-line treatment modalities were based either on polychemotherapy or on zidovudine combined with pegylated interferon alpha. Hematopoietic stem cell transplantation as a consolidation treatment, has been proposed to 7 patients. The 4-year survival was 11.4% for the entire study population with 0% and 11% for the lymphoma

and acute group, respectively. The median survival time was 104 days for the acute group and 120 days for the lymphoma group (p = 0.37). The cause of death was due first to infections (29%) then to disease (25%). Male sex, the presence of "B" signs at diagnosis and hypercalcemia were associated with a poor prognosis with a hazard (HR) ratio of 1.4 (p= 0.479), 1.3 (p=0.201) and 1.6 (p=0.383) respectively. Conversely, deworming appeared to be a good prognostic factor with a HR of 0.680 (p = 0.394).

**Conclusion:** This study provided real-life data from ATL patients in French Guiana, a high-income territory in a low-income part of the world. It shed light on the cultural and geographic diversity of the patients in this region with a clear predominance of Maroons. Patients presented with a younger age and the prognosis was poorer than expected, compared to Japanese patients.

**Table 1:** Clinical and biological characteristics of patients with ATL at diagnosis

| Characteristic | Unit | Patients evaluated | All | ATL subtypes according to Shimoyama's classification | | | |
|---|---|---|---|---|---|---|---|
| | | | | Acute | Lymphoma | Chronic | PCT-ATL |
| Female sex | N (%) | 41 (100%) | 23 (56%) | 16 (70%) | 5 (36%) | 1 (100%) | 1 (100%) |
| Age at diagnosis | Median (range) years | 41 (100%) | 54.5 (17-88) | 54 (30-88) | 61(17-78) | 59 | 42 |
| Leukocytes | G/L | 40 (97%) | 12 (1.6-120) | 44.4 (3.9-120) | 7 (1.6-15) | 6.8 | 2.4 |
| Abnormal lymphocytes | N/mm 3 (% of Leukocytes) | 34 (83%) | 2873 (22.1%) | 35 000 (48.9%) | 0 | 0 | NA |
| Creatinine at diagnosis | µmol/L | 40 (97%) | 76 (42-403) | 89 (44-403) | 73.5 (42-137) | 55 | 61 |
| LDH | UI/L | 29 (71%) | 790 (221-12739) | 820 (221-3351) | 703.5 (286-12739) | 367 | 683 |
| LDH > ULN | % | 29 (71%) | 93.1% | 88.2% | 100% | 100% | 100% |
| Calcemia | mmol/l. | 40 (97%) | 3.1 (2.09 – 6.5) | 3.66 (2.3 – 6.5) | 2.5 (2.09 – 4.8) | 2.51 | 2.48 |
| Hypercalcemia at diagnosis | % | 40 (97%) | 55% | 69.5% | 42.8% | 0 | 0 |
| Calcemia maxima | mmol/L | 40 (97%) | 3.61 (2.3 – 6.8) | 4.15 (2.3 – 6.8) | 3.31 (2.36 – 5.49) | 2.51 | 2.52 |

Abbreviations: LDH: lactate dehydrogenase; ULN : upper limit of normal

## 575 PREVALENCE AND CARDIOVASCULAR OUTCOME OF CLONAL HEMATOPOIESIS IN MEN LIVING WITH HIV

**Sergiu Pasca**[1], Shiyu Wang[1], Susan Langan[1], Aparna Pallavajjalla[1], Lisa Haley[1], Christopher Gocke[1], Wendy Post[1], Matthew Budoff[1], Sabina Haberlen[1], Todd Brown[1], Richard F. Ambinder[1], Joseph B. Margolick[1], Lukasz P. Gondek[1]
[1]*The Johns Hopkins University, Baltimore, MD, USA*

**Background:** Cardiovascular disease (CVD) is more common in people living with HIV (PLWH) than in HIV-uninfected (HIV-) men and may be related to abnormal immune activation. Clonal hematopoiesis (CH), a condition representing the expansion of mutated hematopoietic clones, has been associated with CVD events and systemic inflammation in the general population. We investigated whether CH was more common in PLWH compared to HIV- men and whether CH was associated with subclinical coronary atherosclerosis in PLWH.

**Methods:** Study participants were selected from men in the Baltimore-Washington DC center of the Multicenter AIDS Cohort Study (MACS) who had had coronary CT angiography (CTA) and inflammatory biomarker measurement as part of the MACS Cardiovascular Study. To detect CH, DNA extracted from viably frozen peripheral blood mononuclear cells or cell pellets was subjected to targeted next generation sequencing (NGS) which included 70 genes frequently mutated in hematologic malignancies.

**Results:** The current analysis was a cross-sectional study involving 86 (72.9%) PLWH and 32 (27.1%) HIV- men. The median age was 53 and 54 years for PLWH and HIV- men, respectively (p=0.147). Since the minimum size of the biologically relevant CH in PLWH is unknown, we applied variant allele frequency (VAF) cut-offs of >0.5% and >1%. For both cutoffs, CH was significantly more frequent in PLWH than in HIV- men (p=0.012 and p=0.036, respectively) (Fig1A). Moreover, PLWH had a different mutation distribution (Fig1B) and more somatic mutations than HIV- men (p=0.043 and 0.033, respectively) (Fig1C). Since inflammation-mediated complications of CH become more apparent in people with larger clones, we asked whether CH with VAF>1% was associated with CVD in PLWH. Stenosis ≥50% of any of 15 coronary artery segments analyzed was more frequent in PLWH with CH than in PLWH without CH (p=0.032) (Fig1D). This difference remained significant (p=0.017) in a multivariable logistic regression model that adjusted for the Framingham coronary heart disease 10-year risk score. Additionally, in PLWH, CH was not significantly associated with serum levels of CRP, IL1B and IL6.

**Conclusion:** CH was more common in PLWH and was associated with the presence of coronary artery stenosis ≥50% in PLWH. Larger studies are needed to further examine the clinical consequences of CH and may result in better risk stratification and preventive strategies in PLWH.

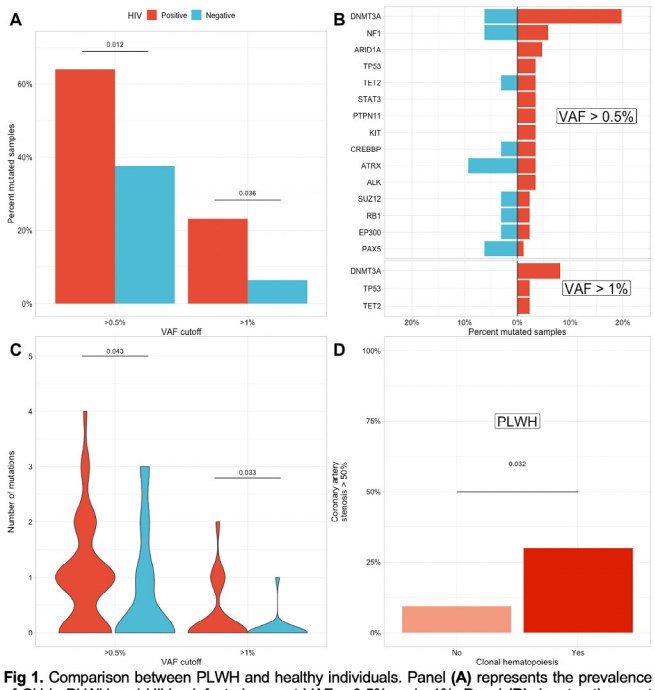



**Fig 1.** Comparison between PLWH and healthy individuals. Panel **(A)** represents the prevalence of CH in PLWH and HIV-uninfected men at VAF > 0.5% and >1%. Panel **(B)** denotes the most commonly mutated genes in PLWH and HIV-uninfected men at VAF > 0.5% and >1%. Panel **(C)** shows the number of mutations in PLWH and HIV-uninfected men at VAF >0.5% and >1%. Panel **(D)** denotes the frequency of coronary artery stenosis ≥ 50% (moderate/severe) in PLWH with or without clonal hematopoiesis.

## 576 CLONAL HEMATOPOIESIS, INFLAMMATION, AND CORONARY ARTERY DISEASE IN PERSONS WITH HIV

New Investigator Scholar

**Andreas D. Knudsen**[1], Andreas Fuchs[1], Alvaro H. Borges[1], Christian Eskeland[1], Sisse R. Ostrowski[1], Joachim Weischenfeldt[1], Marco Gelpi[1], Cavan Reilly[2], James Pankow[2], Kirsten Grønbæk[1], Lars Køber[1], Marius Trøseid[3], Klaus F. Kofoed[1], Susanne D. Nielsen[1]
[1]*Rigshospitalet, Copenhagen, Denmark,* [2]*University of Minnesota, Minneapolis, MN, USA,* [3]*Oslo University Hospital, Oslo, Norway*

**Background:** Persons living with HIV (PLWH) have increased risk of an ageing-related expansion of blood cell subpopulations with specific somatic mutations termed clonal hematopoiesis (CH). CH is associated with both inflammation and cardiovascular disease in uninfected populations. We aimed to investigate the distribution of coronary artery disease (CAD) and explore if CH and inflammatory markers were associated with CAD in older, well-treated PLWH.

**Methods:** PLWH were included from The Copenhagen Co-morbidity in HIV Infection (COCOMO) Study. All COCOMO participants had a plasma sample collected in biobank and were offered a high-resolution research coronary CT angiography. We included all participants with a coronary CT angiography (N=705) in which a subset of 171 randomly chosen participants older than 55 years had targeted gene sequencing performed. CAD severity in CT-scans were categorized as non-obstructive (<50% stenosis) and obstructive (≥50% stenosis). Inflammatory markers IL-6, IL-1β, soluble CD14 and soluble CD163 were analyzed using commercial multiplex assays, and high concentration of an inflammatory marker was defined as above the 75th percentile. Gene sequencing was done using targeted sequencing of 21 CH-associated genes and CH was defined as variant allele frequency >2%.

**Results:** Of 705 included, 77 (11%) were women, mean age was 51 (standard deviation, SD: 11) years, and 669 (95%) had suppressed viral replication. A total of 190 (27%) had non-obstructive CAD and 121 (17%) had obstructive CAD. High levels of IL-6 were associated with higher odds of obstructive CAD (odds ratio, OR:3.24 [2.08, 5.03], P<.001) in unadjusted analyses and after adjusting for age and sex (OR:1.95 [1.19-3.19], P=.008). IL-1β, soluble CD14, and soluble CD163 were not associated with CAD in unadjusted or in adjusted analyses. Among 171 individuals who had gene sequencing performed, 46 (27%) individuals had CH. The most common CH-related mutations were in DNMT3A (n=22, 13%) and TET2 (n=12, 7%). Of individuals with CH, 138 (81%) had no CAD, 21 (46%) had non-obstructive CAD, 9 (20%) had obstructive CAD and 3 (2) had non-diagnostic scans. CH was not associated with CAD in unadjusted or adjusted analyses.

**Conclusion:** More than half of well-treated PLWH had evidence of coronary atherosclerosis and high levels of IL-6 were associated with obstructive CAD. However, no other inflammatory markers were associated with CAD, and CH was not associated with CAD.

## 577 SUBCLINICAL ATHEROSCLEROSIS AND IMMUNE ACTIVATION AMONG US FEMALES VS MALES WITH HIV

**Markella V. Zanni**[1], Borek Foldyna[1], Kenneth Williams[2], Tricia H. Burdo[3], Sara McCallum[1], Sara E. Looby[1], Patrick Autissier[2], Kathleen Fitch[1], Judith S. Currier[4], Michael T. Lu[1], Pamela S. Douglas[5], Heather J. Ribaudo[6], Steven Grinspoon[1]
*[1]Massachusetts General Hospital, Boston, MA, USA, [2]Boston College, Chestnut Hill, MA, USA, [3]Temple University, Philadelphia, PA, USA, [4]University of California Los Angeles, Los Angeles, CA, USA, [5]Duke Clinical Research Institute, Durham, NC, USA, [6]Harvard TH Chan School of Public Health, Boston, MA, USA*

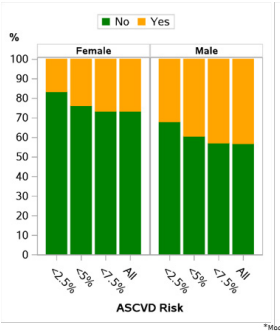
**Background:** Among people with HIV (PWH), sex-differences in presentations of atherosclerotic cardiovascular disease (ASCVD) may be influenced by underlying differences in coronary plaque parameters, immune indices, or relationships therein.

**Methods:** REPRIEVE, a primary ASCVD prevention trial, enrolled ART-treated PWH globally. At study entry, a subset of US REPRIEVE participants underwent coronary CT angiography (CCTA) ± immune phenotyping (N=755 CCTA; N=725 CCTA + immune). We characterized sex-differences in coronary plaque (log binomial regression for a relative prevalence rate (RR)) and immune indices (linear regression) and compared immune-plaque relationships by sex. Unless noted otherwise, analyses adjust for ASCVD risk score.

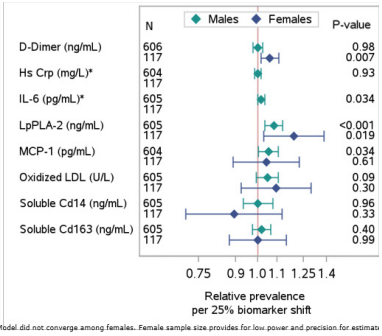
**Results:** The primary analysis cohort included 631 males and 124 females (median age 51 years). ASCVD risk was higher among males (median 4.9% vs. 2.1%) while obesity rates were higher among females (48% vs. 21%). Prevalence of any plaque and of plaque with either visible noncalcified portions and/or vulnerable features (NC/V-P) was lower among females vs. males overall and controlling for ASCVD risk (Fig1A): RR (95% CI) for any plaque 0.67 (0.50, 0.92), RR for NC/V-P 0.71 (0.51,1.00) (adjusted for ASCVD risk and BMI). Among those with any plaque, prevalence of NC/V-P did not differ by sex (P=0.33). Females vs. males showed: 1) higher levels of IL-6, hsCRP, and d-dimer and lower levels of Lp-PLA2 (P<0.001 for all); 2) a lower percentage of total monocytes and a shift toward a higher percentage of inflammatory/intermediate (CD14+CD16+) and patrolling/non-classical (CD14-CD16+) vs. classical (CD14+CD16-) monocyte subsets (P<0.001 for all). Higher levels of Lp-PLA2, MCP-1, and oxLDL were associated with higher plaque (P<0.02) and NC/V-P prevalence (Fig1B), with no differences by sex (interaction P>0.25). Among females but not males, d-dimer was associated with higher prevalence of NC/V-P (Fig1B).

**Conclusion:** Females vs. males with HIV had a lower prevalence of plaque and plaque with visible noncalcified portion and/or vulnerable features, as well as key differences in immune parameters. Immune-plaque relationships differed by sex for d-dimer, but not other tested parameters. Understanding sex-specific immune drivers of subclinical coronary pathology will be key to tailoring ASCVD preventive therapies to PWH.

**A. Prevalence of Plaque with Visible Noncalcified Portions or Vulnerable Features by ASCVD Risk Group among Females vs. Males with HIV**




**B. Relationships between Systemic Immune Indices and Plaque with Visible Noncalcified Portions or Vulnerable Features by Sex**




*Model did not converge among females. Female sample size provides for low power and precision for estimate

## 578 INFLAMMATORY CLUSTERS PREDICT MULTIMORBIDITY AND CVD IN PEOPLE WITH HIV ON ART

New Investigator Scholar

**Padraig McGettrick**[1], Willard Tinago[1], Alejandro A. Garcia[1], Stefano Savinelli[1], Eoin Feeney[1], Eavan G. Muldoon[2], Tara McGinty[2], John S. Lambert[2], Gerard Sheehan[2], Aoife G. Cotter[2], Alan Landay[3], Patrick Mallon[1]
*[1]University College Dublin, Dublin, Ireland, [2]Mater Misericordiae University Hospital, Dublin, Ireland, [3]Rush University Medical Center, Chicago, IL, USA*

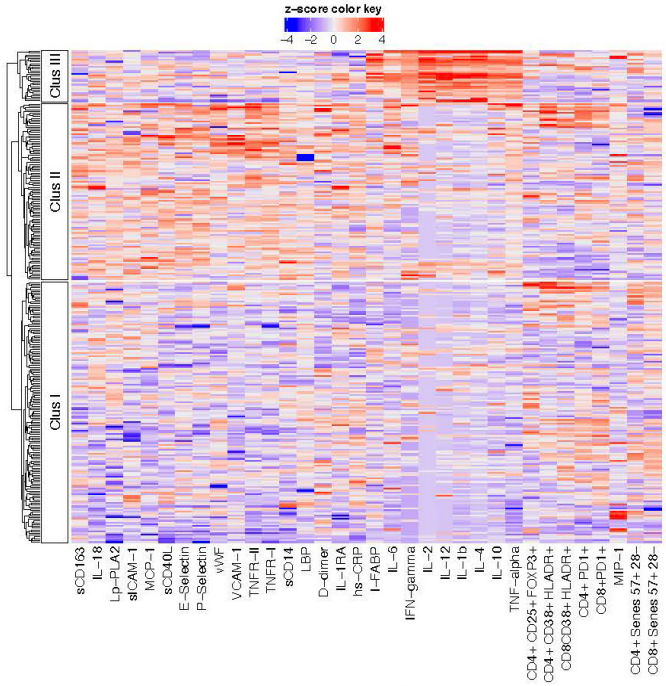
**Background:** People with HIV (PWH) on antiretroviral therapy (ART) are at increased risk of comorbidities, including cardiovascular disease (CVD), with underlying inflammation thought to contribute to excess, unmeasured risk.

**Methods:** The UCD Infectious Diseases Cohort Study recruited PWH on effective ART and analysed 27 biomarkers of systemic, innate and vascular inflammation by chemiluminescence immunoassays and 7 T-cell markers by flow cytometry (CD4+ and CD8+ T-cell senescence, activation, exhaustion and T-regulatory cells). We used principal component analyses and unsupervised hierarchical clustering to partition participants into biomarker-derived clusters and explored associations between clusters and 1) multimorbidity (2 or more of CVD, hypertension, dyslipidaemia, malignancy, osteoporosis, diabetes, kidney, liver, respiratory or psychiatric disease); and 2) CVD, with multivariate models including variables associated on univariate analysis (p<0.1).

**Results:** 277 PWH were included in the analysis [median (IQR) age 44 (39, 50) years, 57.4% male, 45% caucasian, 25.1% current smoker]. Three biomarker derived clusters were identified: cluster 1 (n=148, 53.4%) characterized by lower systemic (TNFa, TNFR1, TNFR2, IFN-gamma, IL-6, IL-1b), vascular (P-selectin, E-selectin, VCAM, ICAM-1) and innate (sCD14, MCP-1) inflammation, cluster 2 (n=100, 36.1%) characterized by higher values of vascular and innate inflammation and cluster 3 (n=29, 10.5%) characterised by high values of markers of T-cell activation and proliferation (IL-1b, TNFa, IL-6, IFN-gamma, IL-10, IL-12, IL-2, IL-4) and microbial translocation (IFABP). There was no significant differences in demographics, HIV or immunological indices between clusters. 77 (27.8%) individuals reported a history of multimorbidity, 13 (5%) with CVD. On univariate analysis both cluster 2 and 3 were associated with multimorbidity compared to non-inflamed cluster 1 (see figure 1b). Cluster 3 was significantly associated with CVD (figure 1c), an association that persisted after adjustment for age, gender, cholesterol and smoking [adjusted odds ratio 7.07 (95% confidence interval 1.28, 38.9), p=0.025].

**Conclusion:** In PWH on ART, individuals can be partitioned into clusters characterised by inflammatory patterns, with clusters of higher inflammation associated with multimorbidity and specifically CVD. Further studies are warranted to examine the utility of bio-profiling populations to identify individuals at high risk of developing CVD for targeted interventions.

(a)



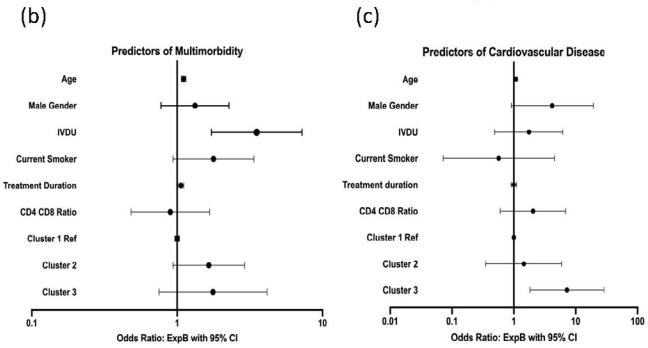



**Figure 1: (a) Characterization of biomarker derived clusters and (b) associations between variables and multimorbidity and (c) CVD on univariate analysis**

IVDU, Intravenous drug use; IL, Interleukin;MCP-1 Monocyte chemoattractant protein; vwf, von willibrand factor; VCAM1, Vascular cell adhesion molecule;TNFR, tumour necrosis factor receptor; LBP, LPS binding protein; IL-1RA, IL 1receptor antagonist; I-FABP,intestinal fatty acid binding protein; MIP-1, macrophage inflammatory protein

## 579 GDF15 IS A MARKER OF HIGH-RISK CORONARY ATHEROSCLEROTIC PLAQUE IN PLWH

New Investigator Scholar

**Léna Royston[1],** Stéphane Isnard[1], Nils Perrin[2], John Lin[1], Brandon Fombuena[1], Manel Sadouni[3], Nicolas Chomont[3], Mohammad-Ali Jenabian[4], Benoit Trottier[5], Jean-Guy Baril[5], Carl Chartrand-Lefebvre[3], Cécile Tremblay[3], Madeleine Durand[3], Jean-Pierre Routy[1]

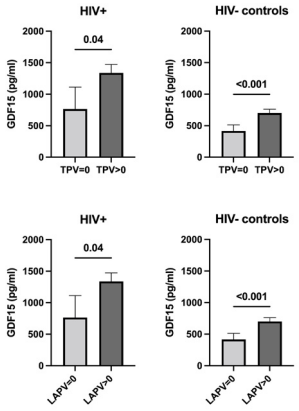
*[1]McGill University Health Centre Research Institute, Montreal, Canada, [2]Montreal Heart Institute, Montreal, Canada, [3]Centre de Recherche du CHUM, Montreal, Canada, [4]Université du Québec à Montréal, Montreal, Canada, [5]Clinique Médicale du Quartier Latin, Montreal, Canada*

**Background:** Despite antiretroviral therapy (ART), people living with HIV (PLWH) experience a high burden of age-related non-AIDS comorbidities. Increased rates of cardiovascular diseases (CVD) and larger subclinical noncalcified coronary plaques at coronary CT angiography have been observed in ART-treated PLWH compared to HIV-uninfected people. Growth differentiation factor-15 (GDF15) is a transforming growth factor-β family cytokine/mitokine, emerging as one of the best markers for poor cardiovascular clinical outcomes in the general population.

**Methods:** We cross-sectionally analyzed plasma of 89 PLWH on ART and 46 controls. We measured two mitochondrial stress-related cytokines/mitokines, GDF15 and fibroblast growth factor 21 (FGF21), and the comorbidity marker soluble urokinase plasminogen activator receptor (suPAR). HsCRP in plasma and HIV reservoir size (integrated HIV DNA) in CD4+ T cells were quantified. All 135 participants had no overt CVD and underwent coronary CT angiography with 3D reconstruction of coronary artery atherosclerotic plaques. Total plaque volume (TPV) and low attenuation plaque volume (LAPV, defined as density < 30 HU) were calculated (in $mm_3$).

**Results:** PLWH and controls had similar age (55 years) and were mostly males (91% and 80% of PLWH and controls, respectively). GDF15 levels were higher in PLWH than in HIV-uninfected controls (934pg/ml vs 480, p<0.001). In PLWH, GDF15 levels were increased in participants with presence of coronary plaque vs without (total plaque: 1037pg/ml vs 764, p=0.04, low-attenuation plaque: 1337pg/ml vs 905, p=0.04), and correlated with TPV (r=0.27, p=0.009) and LAPV (r=0.28, p=0.008). Similarly, among controls GDF15 levels were higher in those with coronary plaque vs without (total and low-attenuation plaque: 640pg/ml vs 416, p<0.001) and correlated with TPV (r=0.62, p<0.001) and LAPV (r=0.60, p<0.001). Only in PLWH, TPV and LAPV also significantly correlated with HIV reservoir size and to hsCRP and suPAR, although to a lesser extent than GDF15. Conversely, FGF21 was not associated with TPV nor LAPV in both populations.

**Conclusion:** In PLWH, plasma GDF15 levels were higher than in HIV-uninfected controls. In both groups, increased GDF15 levels were associated with the presence of coronary artery plaques, in particular low attenuation plaques, which were shown to predict future coronary events. Altogether, GDF15 represents a new marker of high-risk coronary plaques in PLWH.




## 580 ROLE OF RENIN-ANGIOTENSIN-ALDOSTERONE ACTIVATION IN ARTERIAL INFLAMMATION IN HIV

New Investigator Scholar

**Grace Shen[1],** Teressa S. Thomas[1], Allie R. Walpert[1], Kathleen Fitch[1], Christopher R. deFilippi[2], Gail K. Adler[3], Steven Grinspoon[1], Suman Srinivasa[1]

*[1]Massachusetts General Hospital, Boston, MA, USA, [2]INOVA Heart and Vascular Institute, Falls Church, VA, USA, [3]Brigham and Women's Hospital, Boston, MA, USA*

**Background:** Arterial inflammation (AI) remains increased among persons with HIV (PWH) compared to persons without HIV (PWOH) and may contribute to atherosclerotic disease in PWH. Our prior work has shown unique renin-angiotensin-aldosterone system (RAAS) physiology among PWH. We assessed whether lipoprotein-associated phospholipase-A2 (LpPLA2), a key marker of AI, was related to RAAS activation among PWH.

**Methods:** 20 PWH and 9 PWOH followed a controlled, standardized low and liberal sodium diet to simulate a RAAS activated and RAAS suppressed state, respectively. We measured serum LpPLA2 concentrations following both conditions to assess the physiologic dynamics of aldosterone in relation to AI. Comparisons within serostatus group were made using the Wilcoxon Signed Rank test and between serostatus groups using the Kruskal-Wallis test. Univariate analyses were assessed using Pearson's correlation coefficient after log transformation.

**Results:** PWH(age 49±2 yrs, male sex 65%) were of similar age and sex to PWOH, demonstrated good immunologic control(CD4+ count 571.5±72.6 cells/mL, log HIV viral load 1.8±0.2 copies/mL), and had long histories of HIV(18.4±1.5 yrs) and ART use(10.9±1.2 yrs). Aldosterone levels were significantly higher in the HIV vs. non-HIV group in a RAAS activated state(13.8[9.7, 30.9] vs. 9.1[7.4, 12.8] ng/dL, P = 0.02). LpPLA2 levels were significantly higher in the HIV vs. non-HIV group during both the RAAS activated state(237.3[190.1, 276.5] vs. 179.9[132.8, 214.8] ng/mL, P = 0.01) and RAAS suppressed state(196.5[173.3, 240.1] vs. 171.5[151.6, 183.8] ng/mL, P = 0.01). Among PWH but not PWOH, LpPLA2 increased significantly with RAAS activation(P =0.03). LpPLA2 levels measured during the RAAS suppressed state among PWH remained relatively higher than LpPLA2 levels under both conditions among PWOH. LpPLA2 was related to aldosterone during the RAAS activated state(r=0.39, P=0.04) among all participants. LpPLA2 was correlated to visceral fat(r = 0.46, P = 0.04) and systolic blood pressure(r = 0.57, P = 0.01) during a RAAS activated state when an increase in aldosterone was stimulated in HIV. There were no significant correlations demonstrated among PWOH during the RAAS activated state.

**Conclusion:** LpPLA2 is increased during a RAAS activated state in HIV which suggests a potential biologic association between aldosterone and AI. These key data may inform future studies that should test the efficacy of RAAS blockade on AI as a targeted treatment approach for cardiovascular disease in HIV.

## 581 STATIN USE IN ART-TREATED HIV REVEALS AN ALTERED MACROPHAGE TRANSCRIPTOMIC PROFILE

New Investigator Scholar

**Jeeda Ismail[1],** Cheryl M. Cameron[1], Manonmani Kumar[1], Banumathi Tamilselvan[1], Ken Riedl[2], Aya Cannon[2], Emily Bowman[2], Grace A. McComsey[3], Nicholas Funderburg[2], Mark J. Cameron[1]

*[1]Case Western Reserve University, Cleveland, OH, USA, [2]The Ohio State University, Columbus, OH, USA, [3]University Hospitals Cleveland Medical Center, Cleveland, OH, USA*

**Background:** Antiretroviral therapy (ART) treated HIV is associated with an inflammatory profile and increased risk of cardiovascular disease (CVD). Monocytes that home to endothelium and differentiate into macrophages in the vessel wall may contribute to CVD risk in people with HIV (PWH). We reported that statins reduce inflammation in PWH. We hypothesized that rosuvastatin would improve the lipidomes of PWH and reduce the proinflammatory signatures in macrophages.
**Methods:** SATURN-HIV, a placebo-controlled trial [NCT01218802], assessed the effects of rosuvastatin (10 mg) on immune activation in ART-treated PWH. Here, we measured the lipidomes (Lipidyzer platform) of participants at baseline (BL) and at 48 weeks (WK48) of statin or placebo treatment (N=14/group). Participants were demographically similar (placebo:mean 39 years of age, 79% male, 57% African American, AA; statin:43 years, 93% male, 71% AA). Pooled serum samples from statin or placebo-treated individuals at BL or WK48 were added to PBMCs from HIV- donors (N=7) to generate monocyte derived macrophages (MDM). MDM RNA was extracted and sequenced via Illumina TruSeq Stranded Total RNA library kits and NovaSeq system. Using R Bioconductor, we performed differential gene expression (DGE) analysis (LIMMA) and pathway analyses (GSVA). Regression analysis between DEGs and lipids identified genes and pathways that are regulated with lipid changes.
**Results:** Statins reduced several lipid classes and species, including levels of ceramides (CER), and lipids linked to CVD in PWH (CER16:0, 22:0, 24:0, 24:1, $p<0.04$). DGE analysis of MDMs from statin vs placebo paired double contrast revealed a decrease in interleukin signaling, reactive oxygen species, and complement pathways in the statin group. Scavenger and lipid receptors, MSR1 and OLR1, were increased with statins, while chemokine, integrin and JAK-STAT kinase DGE decreased. We compared our top DEGs ($p\leq0.05$) to those from our previous MDM PWH vs HIV- analysis and identified genes that are inversely regulated by statin use. INHBA ($p=0.005$), CD300E ($p=0.0006$), and IL1B ($p=0.03$) were downregulated with statins and upregulated in MDMs from PWH vs HIV- subjects. LDHD, a gene related to lipid processing, was upregulated in the statin group ($p=0.039$) and decreased in PWH vs HIV- subjects.
**Conclusion:** Rosuvastatin in ART-treated PWH may lead to a reduced inflammatory response and CVD risk by downregulating pro-atherosclerotic and immune activation signaling in MDMs. *MJC and NTF equal contribution.

## 582 HIGH-SENSITIVE TROPONINS AND CORONARY CALCIUM SCORE IN OLDER ASIAN HIV

**Pairoj Chattranukulchai**[1], Sarawut Siwamogsatham[1], Hay Mar Su Lwin[2], Tanakorn Apornpong[2], Win Min Han[2], Sivaporn Gatechompol[2], Opass Putcharoen[1], Anchalee Avihingsanon[2]
*[1]Chulalongkorn University, Bangkok, Thailand, [2]Thai Red Cross AIDS Research Centre, Bangkok, Thailand*

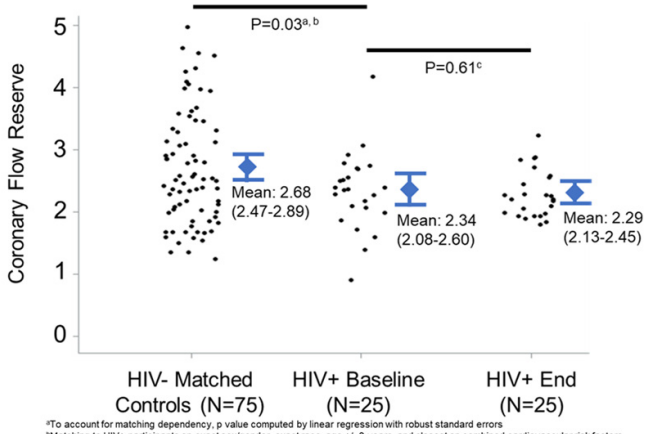
**Background:** High-sensitivity cardiac troponins (hs-cTn), a specific intracellular enzyme of myocardial cells, is suggestive of myocardial cell injury. Elevation of hs-cTn is associated with coronary artery disease (CAD). We sought to explore the relation between hs-cTn and subclinical arteriosclerosis using coronary artery calcification (CAC) scoring, a known surrogate of arteriosclerosis, among people living with human immunodeficiency virus (PLHIV) older than 50 years.
**Methods:** This was a cross-sectional study among 338 PLHIV aged > 50 years on ART without evidence of CAD from Thailand. Non-contrast cardiac computer tomography (CT) for CAC and blood sampling for serum hs-cTn were assessed on the same day. Relationship between the CAC score (Agatston score) and serum hs-cTn levels was analysed using Spearman correlation and logistic regression models.
**Results:** The majority of participants were male (62%) with the median age of 54 years. The median duration of ART was 16 (IQR 13-19) years. The median CD4 cell count was 614 cell/$mm_3$, and 98% had HIV RNA < 50 copies/ml. Of all, 94% had hs-cTnI concentration above the limit of detection (1.9 pg/ml) with a median of 3.7 (IQR 2.7 to 5.2) pg/ml while 85% of them had hs-cTnT concentration above the limit of detection (3 pg/ml) with a median of 5.5 (IQR 3.8 to 8.7) pg/ml. Almost half of the participants had CAC>0 and 16% had CAC ≥ 100. Both hs-cTn concentrations were positively correlated with the Agatston score with the correlation coefficient of 0.28 and 0.27 ($p<0.001$) for hs-cTnI and hs-cTnT, respectively. In multivariate logistic regression analysis, the serum hs-cTnI level was independently associated with an increased odd of having Agatston score≥100 (OR 2.83; 95% CI, 1.69-4.75, p=<0.001).
**Conclusion:** Among the well-controlled HIV-infected aging Asians without established CV disease, the hs-cTnI levels were correlated with subclinical coronary atherosclerosis, measured with CAC. Hs-cTnI may be a potential biomarker to detect CVD early among older PLHIV. Clinical significant of hs-cTnI and CAC > 100 with long-term adverse CV outcomes needs to be prospectively evaluated.

## 583 CORONARY FLOW RESERVE ON DTG/ABC/3TC AT BASELINE AND AFTER SWITCH TO BIC/FTC/TAF

**Daniel M. Huck**[1], Brittany Weber[1], Sean Parks[1], Sanjay Divakaran[1], Jenifer M. Brown[1], Courtney Bibbo[1], Leanne Barrett[1], Camden Bay[1], Laura Kogelman[2], Virginia A. Triant[3], Jacqueline Chu[3], Nina Lin[4], Kathleen Melbourne[5], Paul E. Sax[1], Marcelo Di Carli[1]
*[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Tufts University, Boston, MA, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Boston Medical Center, Boston, MA, USA, [5]Gilead Sciences, Inc, Foster City, CA, USA*

**Background:** HIV infection and abacavir-containing antiretroviral regimens have been associated with increased cardiovascular risk related to endothelial inflammation and dysfunction, key drivers of vascular health. Positron emission tomography (PET) derived coronary flow reserve (CFR), the ratio of peak vasodilator stress to rest myocardial blood flow, is a measure of coronary vascular health that integrates the hemodynamic effects of focal stenosis, diffuse atherosclerosis and microvascular dysfunction and additionally is a powerful marker of cardiovascular risk. The objectives of this study were to compare CFR among people with HIV (PWH) on dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) compared to matched non-HIV controls and to assess whether switching to the non-abacavir regimen bictegravir/tenofovir alafenamide/emtricitabine (BIC/FTC/TAF) would lead to improvement in CFR.
**Methods:** We conducted a prospective, single-arm, multi-center, open-label trial of switching virologically suppressed PWH on DTG/ABC/3TC to BIC/FTC/TAF. We enrolled men over 45 and women over 55 with HIV who were stable on a DTG/ABC/3TC regimen and with at least one coronary risk factor. PWH were also 3:1 matched based on sex/gender, age, race/ethnicity, and cardiovascular risk factors to patients without HIV. PWH underwent baseline PET myocardial perfusion imaging and were then switched to BIC/FTC/TAF for a planned 28-week course followed by a repeat PET scan.
**Results:** 25 enrolled PWH were majority male (68%), cisgender (100%) and Black or Hispanic (56%) with mean age of 57 years. Mean baseline CFR was 2.34 (95% CI 2.08-2.60), statistically significantly lower than the CFR in non-HIV matched patients of 2.68 (95% CI 2.47-2.89, p=0.03, Figure). PWH maintained virologic suppression, and there were no adverse events leading to study drug discontinuation. Mean CFR was 2.29 (95% CI 2.13-2.45) after a mean of 6.3 months of BIC/FTC/TAF treatment, unchanged from baseline (p=0.61, Figure). In exploratory analysis, among enrolled PWH with reduced CFR at baseline (<2.00, N=6), CFR increased significantly from 1.58 (95% CI 1.17-1.99) to 2.02 (95% CI 1.81-2.22, p=0.02) after switch to BIC/FTC/TAF.
**Conclusion:** PWH on DTG/ABC/3TC had statistically significantly lower CFR at baseline compared to matched controls without HIV. There was no significant change in CFR after switching to BIC/FTC/TAF overall; however, those with an abnormal CFR at baseline experienced a significant increase after switch.

**Figure: Coronary flow reserve (CFR) among participants with HIV compared to HIV negative controls, and change in CFR after switching to BIC/FTC/TAF**

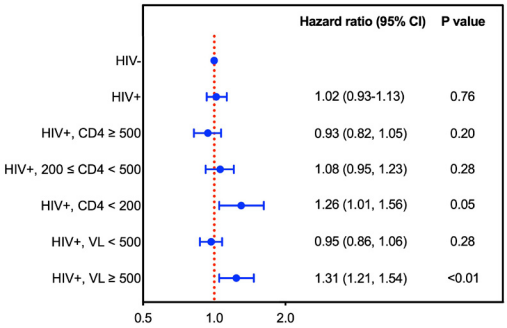



[a]To account for matching dependency, p value computed by linear regression with robust standard errors
[b]Matching to HIV+ participants on exact sex/gender, exact race, age +/- 3 years, and closest on combined cardiovascular risk factors including hypertension, diabetes, current smoking and coronary artery calcium score category (absent, mild, moderate, severe)
[c]P value computed by paired T test. Mean 191 (range 126-302) days on bictegravir/tenofovir alafenamide/emtricitabine (BIC/FTC/TAF)
CFR values are mean (95% confidence interval) and corrected for resting heart rate and blood pressure product.

## 584 HIV INFECTION AND INCIDENT ABDOMINAL AORTIC ANEURYSM AMONG 143,327 VETERANS

**Alexandra M. Filipkowski**[1], Suman Kundu[2], Charles W. Alcorn[3], Joshua A. Beckman[2], Matthew Freiberg[2], Aaron W. Aday[2]
*[1]Fairfield University, Fairfifeld, CT, USA, [2]Vanderbilt University Medical Center, Nashville, TN, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA*

**Background:** People with HIV infection (PWH) have an increased risk of cardiovascular disease. A recent study reported that PWH have a four-fold-higher prevalence of abdominal aortic aneurysm (AAA) compared to people without HIV. However, whether PWH, including never smokers, have an increased risk of incident AAA compared to those without HIV is unknown.
**Methods:** We studied participants from the Veterans Aging Cohort Study, a prospective, observational, longitudinal cohort of veterans with HIV matched 1:2 with veterans without HIV who were free of AAA at baseline. Participants were followed from their first clinic visit on or after 4/1/2003 until development of AAA, death, or censoring on 9/30/2016. We estimated unadjusted AAA incidence rates by Poisson regression with an offset equal to the natural logarithm of follow-up time. Using Cox proportional hazards regression we assessed whether HIV infection, time-updated CD4 T cell counts, and time-updated HIV viral load were associated with incident AAA, defined using ICD-9/ICD-10/CPT codes. Models were adjusted for demographics, cardiovascular risk factors, and substance use. Secondary analyses restricted participants to never smokers.
**Results:** Among 143,327 participants (31% with HIV), there were 2,431 incident AAA events (26% among veterans with HIV) over a median of 8.7 years of follow-up. Overall incident AAA event rates per 1000 person-years were similar among veterans with and without HIV (2.0; 95% confidence interval [CI], 1.9-2.2 and 2.2; 95% CI, 2.1-2.3, respectively). HIV infection was not associated with incident AAA compared to no HIV infection (adjusted hazard ratio [HRadj], 1.02; 95% CI, 0.93-1.13) (Figure). However, in time-updated analyses, there was an increased risk of incident AAA among PWH with CD4 T cell counts <200 cells/mm$_3$ (HRadj, 1.30; 95% CI, 1.05-1.62) and HIV viral load ≥ 500 copies/mL (HRadj, 1.24; 95% CI, 1.05-1.47) compared to those without HIV (Figure). Among never smokers with HIV, time updated CD4 T cell counts <200 cells/mm$_3$ (HRadj, 1.63; 95% CI, 1.02-2.60) but not HIV viral load ≥ 500 copies/mL (HRadj, 1.31; 95% CI, 0.88-1.95) were significantly associated with AAA as compared to never smokers without HIV.
**Conclusion:** HIV infection is only associated with increased risk of AAA among those with low CD4 T cell counts and elevated HIV viral loads. Among PWH without a history of smoking, the risk associated with low CD4 T cell count persists.




Risk of incident AAA using Cox proportional hazards regression. Models adjusted for age, sex, race, hypertension, diabetes, LDL-C, HDL-C, triglycerides, statin use, prevalent CVD, hepatitis C, smoking status, eGFR, hemoglobin, BMI, alcohol abuse. Missing values were imputed using multiple imputation. Stratification was performed using time-updated CD4 count and viral load.

## 585 HYPERTENSION CARE CASCADE DURING COVID IN VETERANS WITH HIV

**Lewis S. Musoke**[1], Sandra Woolson[2], Julie Schexnayder[2], Chris T. Longenecker[1], Elizabeth Strawbridge[2], Hayden Bosworth[3], Puja Van Epps[4]
*[1]Case Western Reserve University, Cleveland, OH, USA, [2]Durham VA Medical Center, Durham, NC, USA, [3]Duke University School of Medicine, Durham, NC, USA, [4]Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA*

**Background:** People with HIV (PWH) are at an increased risk of atherosclerotic cardiovascular disease (ASCVD) compared with those without HIV. Hypertension (HTN) is an important modifiable risk factor for ASCVD, yet HTN management in PWH is suboptimal. The HTN care cascade provides a valuable framework for evaluating HTN care quality. We use data from the Veterans Health Administration (VHA), the single largest U.S. provider of HIV care, to describe HTN care in a nationwide cohort of PWH. We sought to define the HTN care cascade in two years to identify gaps in care and assess impact of the COVID-19 pandemic.
**Methods:** VHA databases were queried to identify Veterans with HIV in care in calendar year (CY) 2019 and 2020. For each CY, we identified cascade steps for HTN care: HTN diagnosis was defined using patient problem lists and validated ICD-10 and SNOMED code-associated outpatient encounters; HTN treatment was defined as active prescription of 1+ antihypertensive drugs; HTN monitoring required at least 2 recorded blood pressure (BP) readings at least 90 days apart; lastly, HTN control was defined as having a last BP recording less 140/90. We compared the care cascade across 2 years to identify potential COVID-19 related changes in HTN care quality. We calculated descriptive statistics using medians and percentages and CY comparisons using Chi-square tests.
**Results:** We identified 31,465 veterans with HIV in the VHA in CY20, 48% were Black, 35% White, 6% self-identified as Hispanic, majority were men (96%) with a median age of 64 years (range 23-96), median body mass index of 27.7 (range 13-74) with 16.5% of Veterans living in rural or highly rural areas. There were no demographic differences between CY19 or 20. In CY19, 12,625 (40%) PWH had a HTN diagnosis, similar to that of CY20 (12,561; 39%). Of these, similar proportions were on treatment for HTN in CY19 (87%) compared to CY20 (88%). Among those on treatment, more patients were monitored (59% vs. 54%; p<0.0001, CI 3.4-6) and of these, more were controlled (59% vs. 54%; p=0.0001, CI 1.8-5.4) for HTN in CY19 compared with CY20. Of all the PWH with a diagnosis of HTN, more were monitored in CY19 (59% vs. 52%; p<0.0001) and had controlled HTN compared with CY20 (67% vs 57%; p<0.0001, CI 8.5-10.9).
**Conclusion:** This nationwide HTN cascade reveals gaps in HTN monitoring and control for Veterans with HIV. The COVID-19 pandemic likely further adversely impacted HTN care delivery in this population.

## 586 HYPERTENSION PREVALENCE AMONG PERSONS LIVING WITH HIV — ZAMBIA, JULY 2020–JUNE 2021

**Jonas Hines**[1], Jose Tomas Prieto[2], Sombo Fwoloshi[3], Peter Minchella[1], Cecilia Chitambala[1], Dalila Zachary[1], Megumi Itoh[1], Khozya D. Zyambo[1], Lloyd B. Mulenga[1], Simon Agolory[1]
*[1]Centers for Disease Control and Prevention, Lusaka, Zambia, [2]Palantir Technologies, Paris, France, [3]Government of Zambia Ministry of Health, Lusaka, Zambia*

**Background:** Hypertension is a major risk factor for stroke and heart disease, both of which are common causes of death in Zambia. Data on hypertension prevalence in Zambia is scarce and generally limited to either specific geographic areas or populations. We sought to measure hypertension prevalence among persons living with HIV (PLHIV) in Zambia using a national electronic health record (EHR).
**Methods:** We did a retrospective cohort study of hypertension prevalence among PLHIV aged ≥18 years in Zambia from July 2020 to June 2021. Data were extracted from the SmartCare EHR, which is in use in over 1,500 health facilities across Zambia that collectively care for between 80-90% of PLHIV on antiretroviral therapy in the country. Hypertension was defined as ≥2 systolic blood pressure readings of ≥140 mmHg or ≥2 diastolic blood pressure readings of ≥90 mmHg during the study period, grade 2 hypertension was defined ≥1 reading with systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg and hypertensive urgency as ≥1 reading with systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg. Multiple logistic regression was utilized to assess associations between hypertension and independent variables.
**Results:** Of 1,249,644 PLHIV active in SmartCare from July 2020 to June 2021, 1,056,556 (84.5%) were aged ≥18 years and had ≥2 visits. Of these, 133,206 (12.6%) had ≥2 blood pressure readings recorded during the study period. The mean patient age was 42.4 years and 64.8% were women. Overall, 35.7% of PLHIV had ≥1 elevated blood pressure reading and hypertension prevalence among PLHIV was 15.1%. Among PLHIV with hypertension, 62% had grade 2 hypertension and 27.9% had hypertensive urgency. Only 11.5% PLHIV with hypertension had an anti-hypertensive medication recorded in their EHR, and of those, 64.6% were still hypertensive. In the adjusted model, the odds of hypertension were greater among men, with increasing age, in urban areas, and among overweight and obese PLHIV.
**Conclusion:** Hypertension was common among a cohort of PLHIV in Zambia. Many PLHIV with hypertension had dangerously high blood pressure and few had documentation of being on antihypertensive treatment. Introduction of

interventions to strengthen the integrated management of non-communicable diseases in ART clinics, including training on the importance of accurate and complete data capture, may help to diagnose and treat hypertension in Zambia while also enhancing future surveillance efforts.

Selected risk factors and association with hypertension* among persons living with HIV (N=133,206) — Zambia, July 2020 – June 2021

| | OR (95% CI) | aOR (95% CI) |
|---|---|---|
| Male (ref = female) | 1.28 (1.24, 1.32) | 1.30 (1.25, 1.35) |
| *Age group* (ref = 18-29 years) | | |
| 30-44 | 2.72 (2.52, 2.95) | 2.48 (2.25, 2.72) |
| 45-59 | 6.67 (6.17, 7.20) | 5.74 (5.22, 6.31) |
| ≥60 | 14.72 (13.53, 16.02) | 13.90 (12.53, 15.43) |
| Urban (ref = rural) | 1.62 (1.56, 1.68) | 1.44 (1.38, 1.5) |
| *BMI* (ref = normal (18.5 – 24.9 kg/m$^2$)) | | |
| Low (<18.5) | 0.66 (0.61, 0.70) | 0.62 (0.58, 0.67) |
| Overweight (25-29.9) | 2.09 (2.01, 2.17) | 1.91 (1.83, 1.99) |
| Obese (≥30.0) | 3.24 (3.11, 3.39) | 2.92 (2.78, 3.08) |

* Hypertension defined as ≥2 systolic blood pressure readings of ≥140 mmHg or ≥2 diastolic blood pressure readings of ≥90 mmHg during the study period

Abbreviations: OR = odds ratio, CI = confidence interval, aOR = adjusted odds ratio, BMI = body mass index, ref = reference category

## 587 ATRIAL FIBRILLATION RISK FACTORS AMONG PATIENTS IN HIV CARE IN THE UNITED STATES

**Robin M. Nance**[1], Joseph A. Delaney[2], James S. Floyd[1], Michael Saag[3], Richard Moore[4], Jeanne C. Keruly[4], Mari M. Kitahata[1], Bridget M. Whitney[1], William C. Mathews[5], Edward R. Cachay[5], Greer Burkholder[3], Amanda Willig[3], Sonia Napravnik[6], Heidi Crane[1], Susan Heckbert[1]
*[1]University of Washington, Seattle, WA, USA, [2]University of Manitoba, Winnipeg, Canada, [3]University of Alabama at Birmingham, Birmingham, AL, USA, [4]The Johns Hopkins University, Baltimore, MD, USA, [5]University of California San Diego, San Diego, CA, USA, [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** Cardiovascular disease risk including atrial fibrillation (AF) is increased for people with HIV (PWH). AF subsequently increases the risk of heart failure and stroke. Despite the potential consequences of AF, relatively little is known about AF risk factors among PWH. This study investigated traditional AF risk factors and HIV-specific variables to understand their association with incident AF.

**Methods:** At 4 sites in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, potential AF cases between 2008-2017 were identified by diagnosis codes. Incident AF was adjudicated by physician review of medical records. In a nested case-control study, we matched each validated incident AF case to 10 controls at the same clinic site using incidence density sampling. For cases and controls, the index date was the AF diagnosis date of the matched case. Potential risk factors were ascertained from lab results, medication prescription records, diagnosis codes, and patient self-report at the closest available date to the index date. Associations of potential risk factors with incident AF were evaluated using multivariable conditional logistic regression. Missing data were rare (<2%) and handled using multiple imputation.

**Results:** This study included 97 incident AF cases and 970 matched controls. Overall, the mean age was 48 years, 21% were female, and 87% were on antiretroviral therapy (ART). In multivariable analyses, traditional cardiovascular risk factors including older age, underlying coronary disease, heart failure, and chronic obstructive pulmonary disease were associated with AF, while treated dyslipidemia, treated hypertension, systolic blood pressure, diabetes, current smoking, and impaired kidney function were not significantly associated. Compared with an ART regimen with a single core class, both non-use of ART at the index date and a regimen with two or more core classes were associated with higher odds of AF (OR 2.93, 95% CI 1.44, 5.96 and OR 1.79, 95% CI 1.003, 3.20, respectively). In sensitivity analyses, adjustment for HIV viral load and CD4 count attenuated the ART regimen associations.

**Conclusion:** PWH were found to share many risk factors for AF that are known in the general population. Additionally, HIV-specific factors of not using ART or using a multi-core ART regimen (which can indicate a longer duration of HIV or more ART treatment experience) were associated with incident AF.

Table 1. Multivariable analysis of risk factors for incident atrial fibrillation or flutter (AF) in CNICS (97 AF cases, 970 controls)

| | Odds ratio | 95% Confidence interval |
|---|---|---|
| Age, per 10 yrs | 1.86 | 1.36, 2.53 |
| Male sex | 2.28 | 0.84, 6.16 |
| Race/ethnicity | | |
| White | Ref. | |
| Black | 0.56 | 0.29, 1.08 |
| Hispanic | 0.35 | 0.14, 0.85 |
| Other | 0.71 | 0.17, 2.92 |
| Treated dyslipidemia | 0.66 | 0.35, 1.24 |
| Treated hypertension | 1.60 | 0.92, 2.78 |
| Systolic blood pressure, per 10 mmHg | 0.99 | 0.84, 1.17 |
| Diabetes Mellitus | 1.73 | 0.92, 3.24 |
| Current smoking | 1.13 | 0.69, 1.85 |
| eGFR, per 30 ml/min/1.73 m$^2$ | 0.75 | 0.51, 1.10 |
| Coronary disease | 2.24 | 1.07, 4.66 |
| Heart failure | 3.32 | 1.55, 7.13 |
| Chronic obstructive pulmonary disease | 2.13 | 1.03, 4.37 |
| Hepatitis C infection | 1.11 | 0.63, 1.97 |
| Antiretroviral therapy at index date | | |
| Regimen with INSTI, NNRTI, or PI core | Ref. | |
| Not on antiretroviral therapy | 2.93 | 1.44, 5.96 |
| Regimen with 2 or more cores | 1.79 | 1.00, 3.20 |

INSTI=Integrase strand transfer inhibitor, NNRTI=Non-nucleoside reverse transcriptase inhibitor, PI=Protease inhibitor, eGFR=Estimated glomerular filtration rate

## 588 ELEVATED METHYLGLYOXAL TRIGGERS HEART FAILURE DURING HIV-1 INFECTION

**Prasanta K. Dash**[1], Fadhel Alomar[1], Jesse Cox[1], Bryan T. Hackfort[1], Howard S. Fox[1], Howard E. Gendelman[1], Santhi Gorantla[1], Keshore R. Bidasee[1]
*[1]University of Nebraska Medical Center, Omaha, NE, USA*

**Background:** Early-onset heart failure (HF) continues to be a major cause of morbidity and mortality in people living with HIV-1 infection (PLWH). More than 40% of PLWH have early-onset HF. Studies suggest that the pathophysiology of this HF is multi-factorial, yet the molecular cause(s) remain poorly defined.

**Methods:** Herein, longitudinal echocardiography (ECHO) was used to assess whether NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice reconstituted with human hematopoietic stem cells (Humanized mice) and infected with HIV-1 and plasma from PLWH, and autopsied cardiac tissues from deceased HIV seropositive individuals, if there is a link between the glycolysis byproduct methylglyoxal (MG) and HF in the setting of progressive HIV-1 infection.

**Results:** Hu-mice developed grade III-IV diastolic dysfunction (DD) at five-weeks post-HIV infection as measured by ECHO with an associated 2-fold increase in plasma MG. At sixteen-weeks of infection, cardiac ejection fraction and fractional shortening declined by 26 and 35%, and plasma MG increased 4-fold higher than uninfected controls. Histopathological and biochemical analyses of cardiac tissues from Hu-mice sixteen-weeks post-infection affirmed MG increase with a concomitant decrease in expression of the MG-degrading enzyme glyoxalase-1 (Glo1). The endothelial cell marker CD31 was found to be lower, and coronary microvascular leakage and myocardial fibrosis were prominent. Increasing expression of Glo1 in Hu-mice five-weeks post-infection using a single dose of an engineered AAV2/9, attenuated the increases in plasma and cardiac MG levels. Increasing Glo1 also blunted microvascular leakage, fibrosis, and HF observed at 16-weeks post-infection, without significant changes in plasma viral loads (VL). In plasma from virally suppressed PLWH, MG was 3.7-fold higher than controls. In autopsied cardiac tissues from seropositive HIV individuals with low VL, MG was 4.2-fold higher and Glo1 was 50% lower compared to uninfected controls.

**Conclusion:** We showed that increasing expression of the primary MG-degrading enzyme Glo-1 in HIV-infected humanized mice using adeno-associated viral gene transfer, not only attenuated the development of HF, but also blunted key mediators of HF including endothelial cell dysfunction, microvascular leakage, inflammation and fibrosis. These new data not only identified a causal link between accumulation of MG and HF in the setting of HIV-infection, but could pave the way for the development of novel therapeutics to mitigate early-onset HF in PLWH.

## 589 ACTIVATED MONOCYTES AND MYOCARDIAL FIBROSIS AMONG PERSONS WITH HIV IN SOUTH AFRICA

New Investigator Scholar

**Tess Peterson**[1], Muki Shey[2], Nomawethu Masina[2], Lye-Yeng Wong[3], Scott Shuldiner[4], Julian Wolfson[5], Stephen Jermy[2], Hadil Saad[2], Achita Singh[2], Mbalabu Lumbamba[2], Graeme Meintjes[2], Ntobeko Ntusi[2], Mpiko Ntsekhe[2], Jason Baker[6]
*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]University of Cape Town, Cape Town, South Africa, [3]Oregon Health and Sciences University, Portland, OR, USA, [4]Kaiser Permanente Southern California, Pasadena, CA, USA, [5]University of Minnesota, Minneapolis, MN, USA, [6]Hennepin Healthcare Research Institute, Minneapolis, MN, USA*

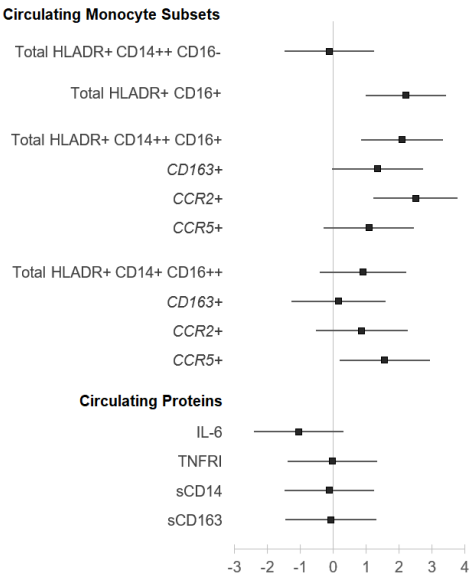
**Background:** Current evidence suggests that, compared to HIV-uninfected persons, ART-treated persons living with HIV (PLWH) have a higher risk of heart failure and underlying pathologies, such as myocardial fibrosis. Immune activation is both a hallmark of chronic HIV infection and intimately involved in the pathology of fibrosis. The objective of this study was to determine if myocardial fibrosis is associated with levels of circulating inflammatory markers and monocyte activation phenotypes among ART-treated PLWH in South Africa (SA).

**Methods:** Participants receiving routine clinical care were enrolled in Khayelitsha—a low-income, densely populated township near Cape Town, SA with an estimated HIV prevalence of 20%. Cardiac magnetic resonance was performed, and degree of myocardial fibrosis was estimated by extracellular volume (ECV) fraction. Plasma concentrations of inflammatory protein biomarkers were measured via enzyme-linked immunosorbent assay, and percentages of circulating monocyte subsets were measured by flow cytometry. Cross-sectional associations were evaluated using linear regression, adjusting for basic demographic and clinical factors.

**Results:** Among 69 black African residents, mean (SD) age was 48 (10) years, 71% were female, 30% were current smokers, 33% were hypertensive, and 57% had prior active tuberculosis infection. Mean (SD) time since HIV diagnosis was 9 (6) years, current CD4 count was 583 (261) cells/μL, CD4 nadir was 266 (207) cells/μL, 45% had prior AIDS, and 36% were virally suppressed for ≥4 years at enrollment. Evidence of left ventricular fibrosis by late gadolinium enhancement was present in 74% of participants, and the mean (SD) ECV fraction was 30.9 (5.9)%. Figure 1 displays the adjusted mean difference in ECV fraction per SD increment in markers of inflammation and immune activation. The largest effect estimates were observed for total CD16+ monocytes (p=0.001); total CD14++ CD16+ (p=0.001); CD14++ CD16+ CCR2+ (p<0.001); CD14++ CD16+ CD163+ (p=0.05); and CD14+ CD16++ CCR5+ (p=0.03). Effect estimates for associations with other measures of inflammation–eg, soluble proteins–were small or imprecise.

**Conclusion:** Among ART-treated PLWH in South Africa, CMR estimates of ECV fraction were positively associated with percentages of non-classical and intermediate monocytes reflecting inflammation and tissue injury. These findings support the need for further research on the influence of monocyte activation in HIV-associated myocardial fibrosis among ART-treated PLWH.

**Figure 1.** Mean difference in extracellular volume fraction per standard deviation increment in circulating monocyte and protein biomarkers (n=69).




Calculated using linear regression, adjusted for age, sex at birth, body mass index, and hypertension. Total HLADR+CD16+ includes both intermediate (CD14++CD16+) and non-classical (CD14+CD16++) monocyte subsets. HLADR=human leukocyte antigen-DR isotype; CD=cluster of differentiation; IL6=interleukin-6; TNFRI=tumor necrosis factor receptor I; ECV=extracellular volume; SD=standard deviation.

## 590 IMPACT OF RHEUMATOLOGIC THERAPIES ON CARDIOVASCULAR OUTCOMES IN PEOPLE WITH HIV

New Investigator Scholar

**Boghuma K. Titanji**[1], Shumpei Nagatomi[2], Julia Gallini[3], Xiangqin Cui[2], Vincent Marconi[1]
*[1]Emory Center for AIDS Research, Atlanta, GA, USA, [2]Emory University, Atlanta, GA, USA, [3]Veterans Affairs Medical Center, Atlanta, GA, USA*

**Background:** Chronic inflammation increases cardiovascular disease (CVD) burden in people with HIV (PWH). There are no effective interventions targeting inflammation to reduce CVD risk in PWH. Rheumatic diseases (RD) are also independently associated with increased risk for CVD. The co-existence of RD and HIV may exacerbate chronic inflammation with implications for CVD outcomes. This study aimed to explore the impact of rheumatologic therapies on CVD outcomes in PWH.

**Methods:** This retrospective study used electronic health record (EHR) data from the Veterans Affairs Medical Center (VAMC) in Atlanta. Of the 5000 eligible participants, 3,930 were included in the analyses excluding individuals who had CVD event before their HIV diagnosis or during the exposure period. The main exposure was type of RD therapy: 1) Multiple medication (>1 type of RD therapy), 2) NSAIDs, 3) Steroids, 4) Immunomodulators, 5) Gout therapy, 6) no RD medications. The main outcome was first occurrence of a CVD event >2 years after HIV diagnosis. Competing risks modelling (Fine and Gray) was used to identify univariate predictors of time to CVD. The multivariate model (adjusted for covariates) used first occurrence of a CVD event as the outcome and rheumatologic therapies as the exposure. All data analyses were performed using SAS Version 9.4.

**Results:** 362 (9.21%) participants had a diagnosis of RD. 660 incident cardiovascular events were observed: myocardial infarction 264 (40%), stroke 110 (16.66%), heart failure 180 (27.27%) and peripheral arterial disease 160 (16.06%). There was a statistically significant association between RD and CVD (OR = 2.67; p<0.001). Compared to the No Medication group, participants exposed to multiple medications (HR=2.058, p=0.0037), NSAIDs (HR=1.730, p=0.0007), Steroids (HR=2.458, p=0.0001), or Gout therapies (HR=3.399, p=0.0001) were significantly more likely to experience a CVD event after adjusting for confounding (age, gender, race, ARVs, VACS index, RD status, hypertension, hyperlipidemia, smoking, and baby aspirin use). The effect of the immunomodulator group was not statistically significant.

**Conclusion:** The coexistence of HIV infection and RD may amplify CVD risk with implications for poor cardiovascular outcomes. Our results suggest that some rheumatologic treatments may exacerbate this risk for PWH. These effects may be different from those observed in HIV-negative cohorts. These findings have implications which warrant further exploration in larger cohorts with appropriate controls.

**Table 1: Hazard Ratios (HR) for time to first CVD event associated with RD medication exposure and CVD risk factors from the multivariate model (Fine and Gray model).**

| Exposure | No. | HR | 95%CI | | P-value |
|---|---|---|---|---|---|
| Multiple medication | 216 | **2.058** | **1.211** | **3.498** | **0.0037** |
| NSAIDs | 2216 | **1.730** | **1.209** | **2.475** | **0.0007** |
| Steroid | 585 | **2.458** | **1.644** | **3.673** | **<0.0001** |
| Immunomodulator | 21 | 1.519 | 0.240 | 9.631 | 0.6187 |
| Gout therapies | 105 | **3.399** | **2.056** | **5.621** | **<0.0001** |
| Smoking (Yes/No) | 811 | 2.115 | **1.499** | **2.984** | **<0.0001** |
| Hypertension (Yes/No) | 744 | 0.906 | 0.655 | 1.256 | 0.5548 |
| Hyperlipidemia (Yes/No) | 337 | 1.449 | 0.898 | 2.338 | 0.1248 |
| Diabetes (Yes/No) | 80 | 0.503 | 0.208 | 1.200 | 0.1244 |
| Aspirin (Yes/No) | 124 | **0.545** | **0.305** | **0.988** | **0.0427** |
| VACS Index | | **1.008** | **1.002** | **1.014** | **0.0064** |
| Age (per year) | | **1.029** | **1.018** | **1.041** | **<0.0001** |
| Male sex | | 1.23 | 0.616 | 2.450 | 0.6680 |

NSAIIDS – Non-Steroidal anti-inflammatory drugs, HR-Hazard ratio, CI-Confidence interval, VACS-Veterans Aging Cohort Study, No.- Number , CVD-Cardiovascular disease, RD – Rheumatologic Disease

## 591 IMPAIRED RESPONSE OF MEMORY TREG TO HDL IS ASSOCIATED WITH HIGHER CARDIOVASCULAR RISK

**Laura O. Atehortua**[1], Carl J. Fichtenbaum[2], W. S. Davidson[2], Mirza Baig[2], Sarah Trentman[2], Claire A. Chougnet[1]
*[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]University of Cincinnati, Cincinnati, OH, USA*

**Background:** Cardiovascular disease (CVD) is an important problem in persons with HIV (PWH). Regulatory T cells (Treg), critical in maintaining immune tolerance, have been implicated in the protection against CVD. Plasma levels of high-density lipoproteins (HDL) are associated with protection from CVD. We recently uncovered interactions between HDL and Treg, showing that internalization of HDL promotes Treg survival through anti-oxidative metabolism. We evaluated whether increased risk of CVD in PWH is associated with decreased circulating effector memory Treg population and responsiveness of Treg to HDL.

**Methods:** Matching triplets of PWH was done based upon age (+/- 10 years), sex, smoking status and CVD risk. Three CVD risk groups were recruited: Group A-Statin use; Group B-ASCVD risk score >9.9% without statin use (high risk); and Group C-ASCVD risk score <5.1% (low risk). Fasting samples were obtained for lipids and CD4+ T cells were purified from PBMCs and cultured with HDL for 24h in serum-free X-VIVO media. Reactive oxygen species (ROS) production were evaluated by flow cytometry in Treg (CD127lowCD25highFOXP3high) subsets: naïve (CD45RAhigh, HLA-DRlow), memory (CD45RAlow, HLA-DRlow) and effector memory (CD45RAlow, HLA-DRhigh).

**Results:** 45 participants had a median age 55 years, 13% female sex, 40% non-white race, 100% with HIV viral load < 200 cpm. Group A median CD4-611 cells/$mm_3$ with ASCVD-12.7%; Grp B median CD4-588 cells/$mm_3$ with ASCVD-13.5%; and Grp C median CD4-676 cells/$mm_3$ with ASCVD-3.9%. HDL decreased reactive oxygen species (ROS) production in memory and effector memory Treg from PWH independently of CVD risk and favoring an anti-oxidative state (Figure 1a). However, when the response to HDL from memory Treg was compared between the three groups, memory Treg from PWH with high CVD risk (Grp B) were less responsive to HDL (Mean=0.59+/-0.07), in comparison with memory Tregs from PWH (Grp C) with low CVD risk (Mean=0.39+/-0.04), having higher production of ROS even in presence of HDL (Figure 1b). Interestingly, the response to HDL of statin treated PWH (Mean=0.48+/-0.03) were similar to PWH with low CVD risk (Figure 1b).

**Conclusion:** Our results suggest that the interaction between HDL and memory Treg may be impaired in PWH with high CVD, increasing the oxidative stress and promoting inflammation in those individuals. This may explain, in part, how inflammation associated with chronic HIV infection alters HDL and Treg resulting in elevation of CVD risk.

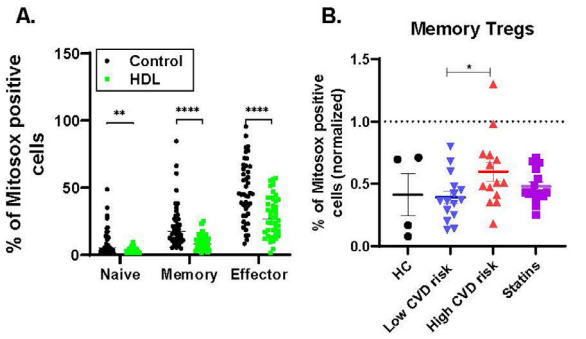



**Figure 1. Memory Treg from PWH with high CVD risk have higher production of ROS in presence of HDL.** Purified CD4+ T cells from PWH under statins treatment (n=15), and with low (n=15) or high CVD risk (n=15) were incubated with HDL for 24h in X-VIVO medium. Percentage of ROS production (Mitosox staining) was evaluated in **A.** naïve (CD45RA$^{high}$, HLA-DR$^{low}$), memory (CD45RA$^{low}$, HLA-DR$^{low}$) and effector memory (CD45RA$^{low}$, HLA-DR$^{high}$) by flow cytometry. Asterisks indicate significant differences (**p<0.005, ****p<0.0001) in two-way ANOVA test **B.** Data are normalized versus the level of Mitosox expression in PBS (control, dotted line). HC: response to HDL from healthy control memory Treg. Asterisks indicate significant differences (* p<0.05) in one-way ANOVA test.

## 592 ASSOCIATION OF IP-10 AND FAT ATTENUATION INDEX IN PWH AND CONTROLS WITHOUT CVD

**Michael L. Freeman**[1], Nivya George[2], Shana Burrows[3], Jean Jeudy[4], Pratik Patel[5], Daniela Moisi[1], Sarah E. Mitchell[2], Mariam Khambaty[4], Kapil Saharia[2], Robert G. Weiss[6], Thomas Mathew[4], Michael M. Lederman[1], Shashwatee Bagchi[2]
*[1]Case Western Reserve University, Cleveland, OH, USA, [2]Institute of Human Virology, University of Maryland, Baltimore, MD, USA, [3]Boston University, Boston, MA, USA, [4]University of Maryland, Baltimore, MD, USA, [5]University of Florida College of Medicine, Gainesville, FL, USA, [6]The Johns Hopkins University, Baltimore, MD, USA*

**Background:** Despite antiretroviral therapy that controls viremia, chronic inflammation is a driver of elevated cardiovascular disease (CVD) risk in people living with HIV infection (PWH). Fat attenuation index (FAI) is a measure of peri-coronary inflammation by coronary computed tomography angiography (CCTA) that independently predicts CVD risk in HIV-uninfected persons and may be an important noninvasive biomarker of asymptomatic CVD in PWH. Whether FAI is associated with soluble chemokines or other inflammatory mediators is unknown.

**Methods:** A cross-sectional study was conducted measuring plasma samples of soluble levels of inflammatory mediators in PWH (n=58) and controls (n=21) without prior CVD who underwent CCTA and had FAI measurements. The associations of white blood cell count, C-reactive protein, CCL2, IP-10/CXCL10, CX3CL1/fractalkine, IL-6, CD14, CD163, RANTES/CCL5, TNFR-I, and TNFR-II with the FAI values of the right coronary artery (RCA) and the left anterior descending artery (LAD) were assessed as tertiles (T) and continuous variables in multivariable regression models adjusted for potential confounders age, sex, race, LDL-c levels, BMI ≥30, and use of lipid-lowering medication. β coefficients define the change in FAI per 1-unit change in IP-10.

**Results:** Several inflammatory factors had significant associations with RCA or LAD FAI in models when adjusted for confounders, including IP-10, CX3CL1, IL-6, TNFR-I, and TNFR-II. IP-10 levels were found to be associated with FAI in all three models tested. Progression from T1 to T3 in IP-10 was associated with worsened LAD FAI among total participants (β=0.661, p=0.047), when adjusted for HIV serostatus (β=0.779, p=0.049), and in a multivariable model adjusting for the other analytes (β=0.957, p=0.001). Progression from T1 to T3 IP-10 was also associated with worsened RCA FAI when adjusted for HIV serostatus (β=0.962, p=0.030) and for all other analytes (β=2.072, p=0.001).

**Conclusion:** Plasma IP-10 levels are associated with both RCA and LAD FAI and thus may be an important systemic indicator of peri-coronary inflammation among people without history of CVD. These findings are consistent with elevated levels of IP-10 seen in PWH and the known links of IP-10 to atherosclerosis in HIV-uninfected individuals. The associations with IP-10 and other inflammatory markers suggest that FAI may be a promising noninvasive biomarker to assess asymptomatic CVD in people with and without HIV.

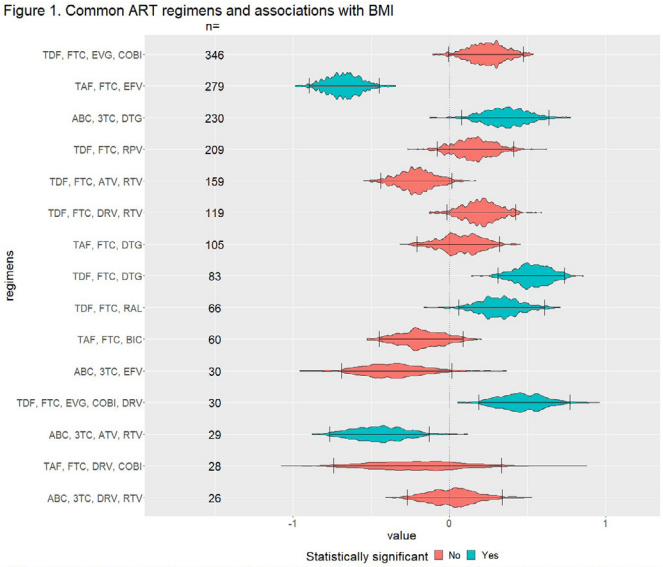
## 593 PREDICTED IMPACT OF ART SWITCH ON BODY MASS INDEX AMONG WOMEN WITH HIV

**Jane O'Halloran[1],** Yuezhe Wang[2], Wei Jin[2], Mary Clare C. Masters[3], Raha Dastgheyb[2], Adaora Adimora[4], Margaret Fischl[5], Deborah Gustafson[6], Igho

Ofotokun[7], Anjali Sharma[8], Amanda B. Spence[9], Phyllis Tien[10], Kathleen Weber[11], Yanxun Xu[2], Leah H. Rubin[2]
*[1]Washington University in St Louis, St Louis, MO, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]Northwestern University, Chicago, IL, USA, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [5]University of Miami, Miami, FL, USA, [6]State University of New York Downstate Medical Center Downstate Medical Center, Brooklyn, NY, USA, [7]Emory University, Atlanta, GA, USA, [8]Albert Einstein College of Medicine, Bronx, NY, USA, [9]George Washington University, Washington, DC, USA, [10]University of California San Francisco, San Francisco, CA, USA, [11]Cook County Health & Hospitals System, Chicago, IL, USA*

**Background:** Newer antiretroviral therapy (ART) has been associated with increased body mass index (BMI) in women with HIV (WWH). Studies are ongoing to examine whether switching ART impacts ART-associated BMI increases. We developed novel machine learning approaches using data from the Women's Interagency HIV Study (WIHS) to determine the contribution of ART on BMI in virally-suppressed WWH. We also demonstrated the clinical utility of these models by predicting the optimal ART regimen to achieve a ≥5% decrease in for BMI in WWH.
**Methods:** Analyses included virally-suppressed (HIV RNA <20 copies/ml) WWH who had visits between 2014-2019. Bayesian machine learning models were developed to estimate the combined effects of different ART regimens on BMI (data from 2014-2019 included in models) while providing information on the effects of prior ART exposure and other risk factors (eg, sociodemographic, behavioral, clinical) on BMI (all available data). Based on the model estimates, we predicted BMI for each woman using acceptable ART regimens from the current DHHS ART guidelines, and compared the predicted BMI with the BMI at their last visit. We then determined the ART regimen that led to BMI reduction of ≥5%.
**Results:** Data from 1533 WWH were included. From the 15 most common ART combinations (≥25 women/regimen [range 26-346 women)), four ART combinations were associated with increased BMI and two with decreased BMI (Figure 1). Exposure time to zidovudine, efavirenz (EFV) and raltegravir, depressive symptoms and recent recreational drug use were associated with lower BMI; tenofovir alafenamide (TAF), rilpivirine and higher CD4 counts were associated with higher BMI. Using the predictive algorithm, a switch in ART was not associated with a predicted BMI decrease of ≥5% in 75% of WWH. Of the 353 WWH predicted to achieve ≥5% BMI decrease following switch, two regimens accounted for 97.5% of the optimal predicted ART regimens - TAF/emtricitabine(FTC)/EFV (51%) and TAF/FTC/atazanavir/ritonavir (46%) although other factors may preclude their use. A switch in BMI category from obese to overweight/healthy or overweight to healthy was predicted in 9%.
**Conclusion:** We identified ART combinations, individual ART drug exposure time, and non-ART factors associated with BMI change in WWH. However, only 25% of the women were predicted to achieve ≥5% decrease in BMI following ART switch. Optimization of other clinical factors may need to be implemented to achieve reductions in BMI among WWH.

Figure 1. Common ART regimens and associations with BMI




TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; EVG, elvitegravir; COBI, cobicistat; TAF, tenofovir alafenamide; EFV, efavirenz; ABC, abacavir; 3TC, lamivudine; DTG, dolutegravir; RPV, rilpivirine; ATV, atazanavir; RTV, ritonavir; DRV, darunavir; RAL, raltegravir; BIC, bictegravir;

## 594 InSTI-RELATED BODY COMPOSITION DIFFERENCES IN CHRONICALLY INFECTED MLWH

**Julie K. Wisch**[1], Sarah Cooley[1], Kevin E. Yarasheski[1], W. Todd Cade[2], Dominic N. Reeds[1], Brittany Nelson[1], Tricia H. Burdo[3], Beau M. Ances[1]
*[1]Washington University in St Louis, St Louis, MO, USA, [2]Duke University, Durham, NC, USA, [3]Temple University, Philadelphia, PA, USA*

**Background:** Substantial body composition and anthropometric alterations have been reported after initiating combined antiretroviral therapy (cART) in people living with HIV. Although weight gain may occur when cART-naïve individuals are placed on integrase inhibitor-based cART (InSTI), the effect of chronic treatment of patients switched to InSTI-based cART is unknown. We characterized a cohort of chronically infected, virologically suppressed (VL < 50 copies/ml) older men (≥ 50 years old) living with HIV (MLWH) with prior exposure to non-InSTI based cART who were switched to InSTI-based cART, and compared their body composition parameters and pro-inflammatory/endocrine profiles to age-matched MLWH on integrase-inhibitor free (non-InSTI) regimens, and to age-matched HIV-seronegative men.
**Methods:** Dual energy x-ray absorptiometry was used to quantify body composition, and plasma proinflammatory/endocrine markers were measured in MLWH (N = 56). Body composition of MLWH was compared to a publicly-available dataset of 450 HIV-seronegative men of similar age distribution. We compared body composition and plasma proinflammatory/endocrine markers between MLWH receiving InSTI-based and non-InSTI cART and assessed the effect of duration of cART on body composition.
**Results:** MLWH had a greater android/gynoid ratio than HIV-seronegative men ($p < 0.001$). InSTI usage in MLWH was associated with lower total visceral adipose tissue mass (VAT) ($p < 0.01$) and greater plasma concentration of insulin-like growth factor-1 (IGF-1) ($p < 0.05$) compared to non-InSTI. Greater duration of cART was associated with lower android-gynoid ratio and trunk to leg ratio ($p < 0.01$).
**Conclusion:** Surprisingly, cART-experienced MLWH who switched to InSTIs had lower total VAT mass and higher plasma IGF-1 concentration than MLWH receiving non-InSTI based cART. These findings suggest that the weight gain associated with InSTI may be most pronounced when initiated in untreated HIV infection and may be less clinically important in cART-experienced populations. Longer duration of infection and age both associated with both lower android/gynoid ratio and lower trunk to leg ratio suggesting that aging and duration of cART impact metabolic risk. Initiation of InSTIs do not appear to have a negative effect on body composition, inflammation, or endocrine function in cART-experienced MLWH.

## 595 PHARMACOGENETICS OF WEIGHT GAIN AFTER SWITCH TO INTEGRASE INHIBITOR-BASED REGIMENS

**David W. Haas**[1], Kunling Wu[2], Katherine Tassiopoulos[2], Todd Hulgan[3], Jordan Lake[4], John Koethe[1], Todd Brown[5], Michael Leonard[1], Sara Bares[6], David Samuels[1], Kristine Erlandson[7]
*[1]Vanderbilt University Medical Center, Nashville, TN, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Vanderbilt University, Nashville, TN, USA, [4]University of Texas at Houston, Houston, TX, USA, [5]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [6]University of Nebraska Medical Center, Omaha, NE, USA, [7]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** Excessive weight gain affects some persons with HIV (PWH) after switch to integrase strand transfer inhibitor (InSTI)-based antiretroviral therapy (ART). In a prior study of 101 PWH who switched from efavirenz (EFV)- to InSTI-based ART, CYP2B6 genotypes (which predict higher plasma EFV levels) were associated with greater post-switch weight gain. Here, we studied associations between CYP2B6 genotype and weight gain after switch from EFV- to InSTI-based ART among participants in ACTG observational cohort studies A5001 and A5322.

**Methods:** Eligible participants switched from EFV- to InSTI-based ART, had available CYP2B6 genotype data, and had weight data at least once from 4 weeks to 2 years after switch. Multivariable linear mixed effects models were fit to assess relationships between CYP2B6 metabolizer group and estimated slope of weight change. Potential confounders considered included age at switch, sex, race/ethnicity, parent ACTG study, body mass index at switch, specific InSTI, CD4+ T-cell count at nadir and at switch, history of smoking or diabetes, years of prior D4T/DDI/ZDV, percent follow-up time pre-switch with HIV-1 RNA <200 copies/mL, and psychiatric medications at switch. Variables that changed unadjusted effect estimates by ≥10% were retained.

**Results:** 174 eligible participants switched ART from 2007 to 2019, with 80 normal, 75 intermediate, and 19 poor CYP2B6 metabolizers; 147 males and 27 females; 93 White, 51 Black, and 27 Hispanic participants; 70 switched to dolutegravir (DTG), 55 to raltegravir (RAL), 41 to elvitegravir (EVG), and 8 to bictegravir. Weight increased in all 3 CYP2B6 groups. Overall, we found no consistent association between CYP2B6 group and rate of weight gain among all participants, or when stratified by sex, race/ethnicity, or InSTI. When limited to 153 participants with HIV-1 RNA <200 copies/mL at time of switch, the rate of weight gain was greater in in CYP2B6 poor than in CYP2B6 normal metabolizers, and within each of 8 subgroups (male, female, white, black, Hispanic, DTG, EVG, and RAL analyzed separately). Only in Hispanic and EVG subgroups was $P < 0.05$. CYP2B6 intermediate metabolizer status was not consistently associated with rate of weight gain.

**Conclusion:** CYP2B6 poor metabolizer genotype was associated with greater weight gain after switch from EFV- to InSTI-based ART, but results were inconsistent. Weight gain in this setting is likely complex and multifactorial.

## 596 WEIGHT CHANGE FOLLOWING SWITCH TO DOLUTEGRAVIR IN RURAL KENYA

New Investigator Scholar

**Matthew D. Hickey**[1], Erick Wafula[2], Lucas Godoy Garraza[3], Sabina Ogachi[2], Gordon Orori[2], Richard O. Adede[2], Maya L. Petersen[4], Diane V. Havlir[1], Laura B. Balzer[3], James Ayieko[2]
*[1]University of California San Francisco, San Francisco, CA, USA, [2]Kenya Medical Research Institute, Nairobi, Kenya, [3]University of Massachusetts Amherst, Amherst, MA, USA, [4]University of California Berkeley, Berkeley, CA, USA*

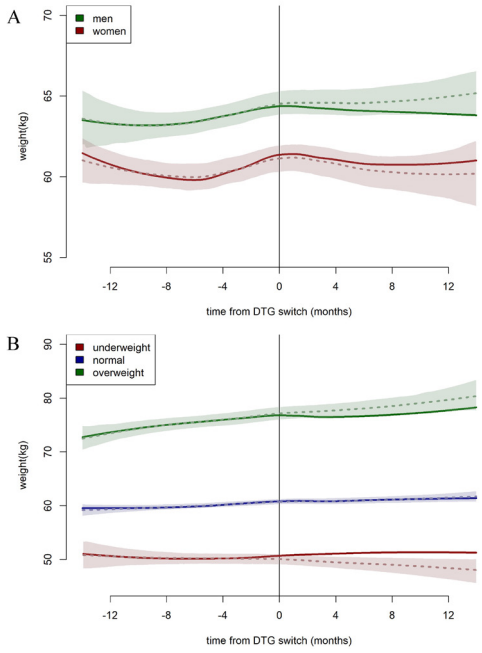
**Background:** Switch to dolutegravir (DTG) in treatment-experienced people living with HIV (PLH) may lead to excess weight gain in high income settings. There are limited data on weight changes following switch to DTG in rural low-income settings with lower prevalence of obesity.

**Methods:** We conducted a retrospective cohort study at eight rural HIV clinics in western Kenya to evaluate weight changes following switch to DTG. We included PLH ≥25 years old who switched before 1/1/2020, were on ART for at least one year prior to switch, & had weight measured at switch & within 14 months pre & post-switch. Using pre-switch data & linear mixed models, we predicted the post-switch weight trajectory for each participant if they had not switched to DTG, adjusting for sex, age, pre-switch regimen, & time. We contrasted the observed vs. predicted post-switch weight change with inference via non-parametric bootstrap.

**Results:** We included 2838 PLH who switched to DTG/TDF/3TC (median age 48 years, 50% female). Median ART duration at switch was 6.6 years (IQR 4.4-9.1). At switch, 11% were underweight (BMI <18.5 kg/m$_2$), 69% normal weight (BMI 18.5-24.9 kg/m$_2$), 16% overweight (BMI 25-29.9 kg/m$_2$), & 4% obese (BMI ≥30 kg/m$_2$). Pre-switch, 99.8% were on an NNRTI (EFV/NVP); NRTIs were TDF/3TC (65%, n=1864), AZT/3TC (26%, n=731), or d4T/3TC (9%, n=260). Among those with a measured pre-switch viral load (n=743), 95% were suppressed (<200 copies/mL). Mean 12-month weight change was 0.8 kg pre-switch & 0.4 kg post-switch. Observed 12-month post-switch weight was 0.5 kg less than predicted (95%CI -0.9 to -0.1) based on pre-switch weight trajectory, and only 0.2 kg less than predicted (95% CI -0.7 to 0.4) among those on TDF pre and post-switch. Restricting to those on TDF throughout, observed 12-month weight was: more than predicted for underweight (2.9 kg, 95% CI 1.3 to 4.5); similar to predicted for women (0.6 kg, 95% CI -0.2 to 1.3), pre-switch suppressed (-0.8 kg, 95% CI -1.9 to 0.3), & normal weight (-0.1 kg, 95% CI -0.7 to 0.5); and less than predicted for men (-1.0 kg, 95% CI -1.6 to -0.3) & overweight/obese (-1.9 kg, 95% CI -3.2 to -0.6).

**Conclusion:** In contrast to reports of weight gain following switch to DTG in high-income settings, we observed slightly less weight increase than predicted based on pre-switch trajectory among ART-experienced adults in rural Kenya. When restricting to those on TDF pre and post-switch, switch from NNRTI to DTG was not associated with weight gain except in those underweight at switch.

Average predicted (dashed) and observed (solid) weight by month from DTG switch among those on TDF throughout, stratified by sex (A) and BMI category (B).




## 597 MACHINE LEARNING ALGORITHM TO PREDICT >5% WEIGHT GAIN IN PWH SWITCHING TO InSTI

**Giovanni Guaraldi**[1], Federico Motta[1], Jovana Milic[1], Sara Barbieri[1], Licia Gozzi[1], Emanuele Aprile[2], Michela Belli[2], Maria Venuta[2], Gianluca Cuomo[2], Federica Carli[2], Giovanni Dolci[2], Vittorio Iadisernia[2], Giulia Burastero[2], Cristina Mussini[1], Federica Mandreoli[1]
*[1]University of Modena and Reggio Emilia, Modena, Italy, [2]Azienda Ospedaliera Universitaria Policlinico di Modena, Modena, Italy*

**Background:** Weight gain (WG) is a well-described phenomenon in PWH starting or switching ART. Machine learning (ML) methods is a tool of P4 medicine (Predictive, Preventive, Personalized & Participatory) and can generate models to identify patients at risk of WG. The objective was to develop an ML algorithm that predicts a 9-month WG≥5% in PLWH switching to InSTI with/without TAF.

**Methods:** This was an observational study that comprised ART-experienced PWH attending Modena HIV metabolic clinic from 2004 to 2020. The patients' medical, HIV and ART data were partitioned in an 80/20 training/test set to generate predictive models. A ML model was used to leverage a hybrid approach where clinical expertise is applied along with data-driven analysis. The study outcome was the prediction at 9 months of weight change with a cut of 5%: at any patient visit (model 1) and in the subset of PWH switching to InSTI with/without TAF (model 2). 9-month prediction was chosen as being the minimum time occurring between any two given visits in the 95% of the cases. A robust

implementation of linear regressor algorithms were able to predict weight gain/loss while tolerating missing data. Intelligible explanations were obtained through Shapley Additive exPlanations values (SHAP), which quantified the positive or negative impact of each variable included in each model on the predicted outcome. A measure of effectiveness (E-measure) was chosen as a performance metric, because unlike accuracy it can penalize errors, particularly underestimation ones.

**Results:** A total of 2817 patients contributed to generate 10877 observations, which allowed construction of 2 predictive models based on 44-variables including anthropometric, HIV and laboratory biomarkers. At last observation median age was 51 years (IQR 11); 70% were male. Median CD4 nadir was 200 cells/μL (IQR 217), current CD4 was 659 cells/μL (IQR 372), 97% had undetectable VL and time since HIV diagnosis was 20 years (IQR 13). Median BMI was 23.4 (IQR 4.5) and 5.8% had obesity. The highest ranked variables used to train the models were weight at time of prediction and the ones depicted in the figure. Model 1 had accuracy of 84.4% and 83.9% E-measure; model 2 had accuracy of 84.4% and 86.4% E-measure.

**Conclusion:** We developed a ML tool with a remarkable E-measure that may assist clinicians in decision-making and shift HIV care towards a P4 medicine. Immune-metabolic variables were more relevant than ART switching in the prediction of WG.

## 598 48-WEEK BODY COMPOSITION CHANGES IN PLWH SWITCHING FROM 3DR TO DTG + 3TC: DOLAM STUDY

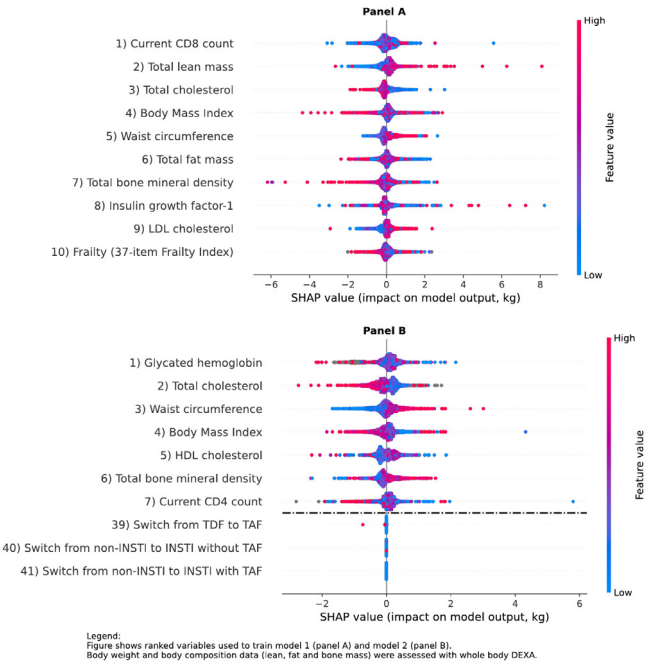
**Esteban Martinez**[1], Elisa de Lazzari[1], Adrià Curran[2], Pere Domingo[3], Eugenia B. Negredo[4], Nadia Abdulghani[5], Jose M. Gatell[6], Jose L. Blanco[1]
*[1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]Hospital Vall d'Hebron, Barcelona, Spain, [3]Hospital Sant Pau, Barcelona, Spain, [4]Hospital Germans Trias i Pujol, Barcelona, Spain, [5]Aalborg University Hospital, Aalborg, Denmark, [6]ViiV Healthcare, Brentford, UK*

**Background:** In DOLAM study, 48-week weight change from baseline increased significantly in DTG+3TC (2DR) arm (mean change 1·6 kg [95% CI 0·9 to 2·4], p<0·0001) but not in triple therapy (3DR) arm (0·1 kg [−0·6 to 0·8], p=0·78). The difference between 2DR versus 3DR in mean weight change at 48 weeks was 1.5 kg (95% CI 0·5 to 2·5, p<0.005). A pre-planned dual-X-absorptiometry (DXA) sub-study aimed to assess 48-week body composition changes.

**Methods:** At baseline and at week 48 weight, height, and whole body, lumbar and hip DXA scans (Lunar iDXA) were performed to assess BMI, body fat, body lean mass and bone composition, respectively. Changes in DXA parameters over time were assessed by random-effect regression models with time, treatment group and their interaction as covariates and adjusted by backbone and 3rd drug at baseline, age and sex. In order to improve residuals distribution, each parameter was transformed into natural logarithm, thus the regression coefficients represent the relative change in the geometric mean (equivalently, median) of the untransformed variable.

**Results:** One hundred and eighty (68%) out of 265 participants contributed to the sub-study. Baseline characteristics did not differ between groups and from those of the main study. At 48 weeks, 33% in 3DR and 45% in 2DR were overweight or obese (P=0.022). Body fat change in 2DR vs 3DR was 1.04 (95%CI 0.94- 1.14) (P=0.451). Limb fat change in 2DR vs 3DR was 1.04 (95%CI 0.93- 1.15) (P=0.511). Trunk fat change in 2DR vs 3DR was 1.17 (95%CI 0.93- 1.47) (P=0.182). Body lean mass change in 2DR vs 3DR was 0.98 (95%CI 0.92- 1.03) (P=0.418). Limb lean mass change in 2DR vs 3DR was 0.99 (95%CI 0.94- 1.03) (P=0.584). Trunk lean mass change in 2DR vs 3DR was 0.99 (95%CI 0.97- 1.02) (P=0.620). Spine BMD change in 2DR vs 3DR was 0.0014 (95%CI-0.0094-0.0121) (P=0.804). Total hip BMD change in 2DR vs 3DR was 0.0009 (95%CI-0.0159-0.0140) (P=0.903).

**Conclusion:** Although there were more overweight or obese PLWH at 48 weeks in 2DR vs 3DR, we were unable to detect significant changes in body fat, lean mass, or BMD between arms.




Legend:
Figure shows ranked variables used to train model 1 (panel A) and model 2 (panel B).
Body weight and body composition data (lean, fat and bone mass) were assessed with whole body DEXA.

## 599 ADIPOCYTE DIFFERENTIATION AND ANTIRETROVIRAL DRUGS: AN IN VITRO MODEL

**Maria Aurora Carleo**[1], Angelica Perna[2], Pietro Rosario[1], Silvia Mascolo[1], Angela Lucariello[3], Giulia Palmiero[1], Viviana Rizzo[1], Anna Maria Rossomando[1], Alfonso Baldi[4], Antonio De Luca[4], Paolo Maggi[4], Vincenzo Esposito[1]
*[1]AORN dei Colli, Naples, Italy, [2]University of Molise, Campobasso, Italy, [3]Department of Sport Sciences and Wellness, University of Naples Parthenope, Naples, Italy, [4]University of Campania Luigi Vanvitelli, Naples, Italy*

**Background:** The Integrase Strand Transfer Inhibitors (InSTI) class of drugs is characterized by a good tolerability profile and a relatively high genetic barrier to HIV drug resistance. However, several studies reported greater weight gain among persons receiving InSTI-based regimens for initial therapy as compared to protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens. These studies could be affected by several potential biases, because of the large number of metabolic comorbidities affecting these patients together to high risk of pharmacological interactions. Since adipocyte differentiation recognizes an important regulatory checkpoint by two families of transcription factors, the CCAAT/enhancer-binding proteins (C/EBPs) and the peroxisome proliferator-activated receptors (PPARs), the evaluation of the expression of adipocyte differentiation markers, such as PPAR-γ and C/EBP-α, is routinely used to evaluate fat tissue differentiation and it has been already assessed to investigate adipocyte differentiation in studies on HIV infected patients.

**Methods:** We used the 3T3-L1 cells in vitro model of adipogenesis to investigate the effects on adipocyte differentiation of the newer NRTI, tenofovir alafenamide fumarate (TAF), alone or in combination with the four InSTIs, raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG) and bictegravir (BIC). Expression levels of PPARɣ and C/EBPα, and the intracellular lipid accumulation by Red Oil staining, were used to monitor adipocyte differentiation.

**Results:** Compared to the control, RAL, EVG, DTG and BIC were all able to increase adipogenesis, being RAL and ELV somehow more efficient, while TAF slightly inhibited adipogenesis. When used in combination with the other InSTIs, TAF was able to reduce the adipogenic effects of all the four drugs. This effect was more evident when TAF was used in combination with DTG and BIC (Figure 1).

**Conclusion:** Several clinical data suggest that therapy with InSTIs could determine weight gain, especially if associated with TAF. Our results confirm that InSTIs could increase adipogenesis, while, on the other hand, in our 3T3L1 cells in vitro model of adipogenesis, TAF shows an inhibitory effect, being able to effectively contrast the increased adipogenesis caused by other InSTIs, in particular DTG and BIC. Taken together, these evidences are suggestive for an antagonistic effect on adipocyte differentiation by different antiretroviral drugs routinely used in therapeutic association.

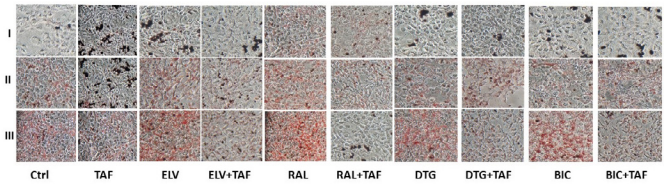
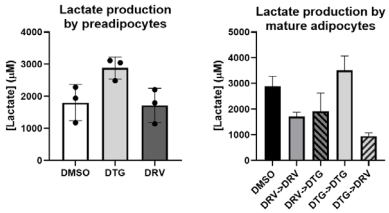



Figure 1 - 3T3L1 Red oil staining according to different steps of adipocyte differentiation and different antiretroviral drugs.

## 600 METABOLIC PERTURBATIONS BY INTEGRASE INHIBITORS IN DIFFERENTIATED HUMAN ADIPOCYTES

**R. Taylor Pickering**[1], Kaitlin M. Soden[1], Archana Asundi[1], Nina Lin[1]
*[1]Boston Medical Center, Boston, MA, USA*

**Background:** Antiretroviral therapies (ART) have diverse effects on adipose tissue biology, clinically observed through changes in weight and fat distribution with ART initiation or switch. The mechanisms that underlie these changes are incompletely understood, especially for newer classes of ART such as integrase-inhibitors (InSTIs). Thus, we sought to examine the effects of modern ART regimens on aspects of adipocyte biology related to weight gain
**Methods:** We established cultures of human preadipocytes and newly differentiated adipocytes from HIV uninfected individuals to examine effects of an InSTI; Dolutegravir (DTG), compared to a protease inhibitor; Darunavir (DRV). For experiments on mature adipocytes, cells were differentiated for 7 days using an adipogenic medium. Adipocytes were switched to a maintenance media and treated with DMSO (Control), DTG, 3.1µg/mL, or DRV, 11.8µM at day 7. After 7 days, cells were maintained or switched to other ART until day 21. Experiments examining preadipocyte responses and effects on adipogenesis initiated treatment during proliferation of precursors, and continued throughout differentiation. Triglyceride content, lactate production and lipolysis were assessed by enzymatic assay and normalized to DNA content. Adipogenic gene expression was assessed using qPCR, and adipokine secretion was determined with ELISA. Oxygen consumption (OCR) and extracellular acidification rates (ECAR) were determined using Seahorse.
**Results:** Exposure to DTG and DRV did not alter cell viability regardless of treatment regimen. Exposure to DTG increased lactate production between 1.3 and 2-fold in both preadipocytes and adipocytes ($p<0.05$) and this increase was reversed in adipocytes when switched to DRV (Image). Accordingly, both basal and maximal OCR were decreased ~15% in cells treated with DTG with corresponding increases in ECAR. DTG exposure in preadipocytes prior to and during differentiation increased expression of PPARγ, a late adipogenic marker (1.5 fold, $p<0.05$) but also suppressed triglyceride accumulation without altering rates of lipolysis. Additionally, cells treated with DTG decreased secretion of leptin and adiponectin.
**Conclusion:** The observed increases in lactate production and decreased oxygen consumption in preadipocytes and adipocytes treated with DTG indicate impairments in mitochondrial function. These alterations in metabolism combined with suppression of key regulatory adipokines may help explain the increased weight gain observed in individuals taking InSTIs.




## 601 DOLUTEGRAVIR REVERSIBLY INDUCES MITOCHONDRIAL FRAGMENTATION AND TOXICITY IN VITRO

New Investigator Scholar

**Loïc C. Caloren**[1], Abhinav Ajaykumar[1], Tetiana Povshedna[1], Anthony Hsieh[1], Marie-Soleil R. Smith[1], Pierre Becquart[1], Jacqueline A. Quandt[1], Judy M. Wong[1], Helene C. Cote[1]
*[1]University of British Columbia, Vancouver, Canada*

**Background:** Despite the success of ARVs in suppressing HIV, drug toxicity remains an area of concern. Older ARV classes, such as NRTI and PI, can deplete mitochondrial DNA (mtDNA), affect mitochondrial function, and increase mitochondrial reactive oxygen species (mtROS). These effects may be mitigated by human telomerase reverse transcriptase (hTERT), which can translocate to mitochondria, where it provides protection from ROS-induced damage. Newer integrase strand transfer inhibitors (InSTIs), such as Dolutegravir (DTG) and Raltegravir (RAL), show excellent clinical tolerance. However, there is emerging evidence of possible off-target effects, such a weight gain, with potential mitochondrial etiology given their role in metabolism. Our objective was to evaluate cellular and mitochondrial toxicities of first line InSTI-containing ARV regimens and determine whether hTERT has a protective effect.
**Methods:** Telomerase-independent SV40-transformed human lung fibroblasts (WI-38 VA13) were transduced to express hTERT with and without its mitochondrial targeting signal (MTS). Three isogenic cell lines (–hTERT, +hTERT–MTS, and +hTERT) were exposed to seven distinct (NNRTI, PI, or InSTI-based) ARV regimens at pharmacological concentrations (1X $C_{max}$) for nine days, followed by recovery in drug-free media for six days. n=6 independent sets. After both treatment and recovery, mitochondrial mass, intermembrane potential, ROS, and cellular apoptosis were quantified using flow cytometry. Mitochondrial images were captured by fluorescence microscopy and the recently developed neural network analysis tool MitoSegNet, was used to quantify differences in mitochondrial morphology.
**Results:** Cells exposed to DTG-containing regimens had increased apoptosis, mtROS, and mitochondrial mass, compared to both 0.1% DMSO controls (all $p\leq0.034$) and non-DTG (including RAL)- containing regimens (all $p<0.001$). DTG exposure increased mitochondrial area, perimeter, eccentricity, branch number and length compared to non-DTG regimens (all $p\leq0.005$). Although hTERT may mitigate some PI-induced effects, it did not protect against DTG. All observed alterations were reversed upon ARV removal.
**Conclusion:** Taken together, our findings suggest that DTG-containing regimens induce mitochondrial toxicity and fragmentation of mitochondrial networks, something not seen with RAL. Given that HIV treatment is life-long and the global use of DTG, further investigations are warranted to understand the mechanisms and long-term effects of these toxicities.

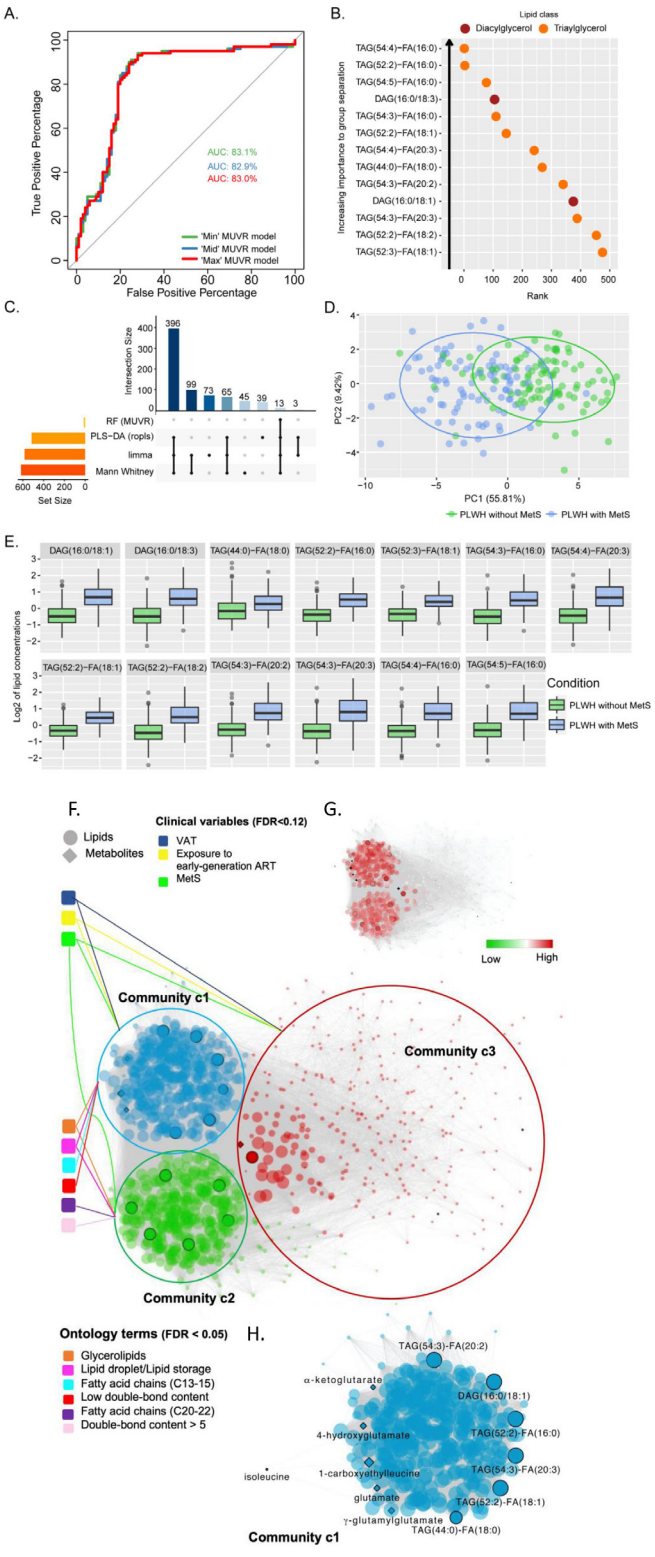
## 602 LIPIDOMICS PROFILE OF METABOLIC SYNDROME IN WELL-TREATED PEOPLE LIVING WITH HIV

New Investigator Scholar

**Sofie O. Villumsen**[1], Rui Benfeitas[2], Andreas D. Knudsen[1], Marco Gelpi[1], Julie Høgh[1], Magda T. Thomsen[1], Daniel Murray[1], Ujjwal Neogi[3], Susanne D. Nielsen[1]
*[1]Rigshospitalet, Copenhagen, Denmark, [2]National Bioinformatics Infrastructure Sweden, Stockholm, Sweden, [3]Karolinska Institute, Stockholm, Sweden*

**Background:** Increased risk of several cardio metabolic diseases has been described even in well-treated people living with HIV (PLWH). Combination antiretroviral therapy (cART), lifestyle and systemic inflammation have all been suggested to play a role. However, the drivers and biological mechanisms of cardio metabolic diseases, including metabolic syndrome (MetS), in the context of HIV infection are still partly unclear. In the present study, we investigated lipidomics profiles associated with MetS in PLWH.
**Methods:** 100 PLWH with MetS and 100 PLWH without MetS were included from the Copenhagen comorbidity in HIV infection (COCOMO) study. The two groups were matched according to age, sex, ethnicity, prior exposure to old generation cART and history of AIDS defining events. Integrative plasma lipidomics and metabolomics analyses were carried out in order to identify lipidomics profiles characterizing MetS in the context of HIV infection. Untargeted lipidomic profiling was performed on venous plasma samples. Differences in lipid profiles between the two groups were tested using standard biostatistical methods combined with machine learning and network analysis techniques.
**Results:** No differences in age (54.4 (9.5) vs 54.6 (8.5), p-value 1.00) and sex (male, 90% vs 90%, p-value 1.00) were found between PLWH with and without MetS. The lipidomic dataset consisted of 917 unique lipid species. Of these, 13 lipids consistently differed between PLWH with and without MetS across all statistical platforms (i.e. Mann-Whitney, limma, PLS-DA and RF). In particular, an increased abundance of the glycerolipids DAGs ($n = 2$) and TAGs ($n = 11$) was described in PLWH with MetS (Figure 1a-e). All the DAGs and 10 out of the 11 TAGs consisted of unsaturated and polyunsaturated long chain fatty acids, respectively. The comprehensive network integration of the lipidomics and metabolomics data suggested interactions between specific glycerolipids structural composition patterns and key metabolites involved in the glutamate metabolism (Figure 1 e-h).
**Conclusion:** We presented data suggesting an increased abundance of the glycerolipids and their structural composition patterns to be associated with MetS in PLWH. Further integration of the key metabolites identified earlier in the same population and clinical data with lipidomics suggest disruption of the

glutamate and fatty acid metabolism to be involved in pathogenesis of MetS in the context of HIV infection.




(a) Performance of random forest (RF) models. Receiver operating characteristic (ROC) curve with area under the curve (AUC) values for the three MUVR models. (b) Important prediction variables separating PLWH without MetS from PLWH with MetS based on lipidomics, diacylglycerol (DAG) and triacylglycerol (TAG). Variables importance on projection (VIP) score plot for the 'Max' MUVR model, where lower rank indicates better group separation, thus better prediction variables in the model 12 classification. (c) Intersection of methods identifying key lipids. UpSet plot showing number of significant lipids found via four statistical methods (RF, PLS-DA, limma and Mann-Whitney U test). Note the 13 lipids (intersection size on the y-axis) simultaneously identified by all four methods. (d) Separation of PLWH without MetS from PLWH with MetS based on identified key biomolecules. Principal component analysis (PCA) on key biomolecules, where lipidomics and metabolomics data were separated by the 13 identified key lipids and 11 identified key metabolites (Table 2). Ellipses show the 95% confidence interval of the data. (e) Boxplot of lipid concentration of the identified key lipids, which consist of DAGs and TAGs. (f) Global network illustrating the associated clinical variables and ontology terms with each community. Network of positive correlations between lipids and metabolites (FDR < 1e-07, Spearman's ρ > 0.38), colored based on the three identified communities, c1 (blue), c2 (green) and c3 (red). Communities are connected with associated clinical variables (FDR < 0.12) and ontology terms (FDR < 0.05). Black circled lipids and metabolites corresponds to identified key lipids and key metabolites (Table 2). (g) Global network illustrating up and down regulated lipids in PLWH with HIV. (h) Local network of community c1 highlighting key biomolecules. Biomolecular correlations within community c1 (FDR < 1e-07, Spearman's ρ > 0.38). Black circled and named biomolecules corresponds to the identified key lipids and metabolites within c1.

## 603 WEEK-48 METABOLIC HEALTH AFTER SWITCH TO DTG/3TC VS CAR BY BASELINE REGIMEN: SALSA

**Debbie Hagins**[1], Cristina Mussini[2], Fujie Zhang[3], Princy N. Kumar[4], Laurent Hocqueloux[5], Nuria Espinosa-Aguilera[6], Christoph Wyen[7], James Oyee[8], Lori A. Gordon[9], Gilda Bontempo[9], Brian Wynne[9], Elizabeth Blair[9], Mounir Ait-Khaled[10], Jean A. Van Wyk[10]

*[1]Georgia Department of Public Health, Coastal Health District, Chatham CARE Center, Savannah, USA, [2]Clinic of Infectious Diseases, AOU Policlinico, and University of Modena and Reggio Emilia, Modena, Italy, [3]Beijing Ditan Hospital, Capital Medical University, Beijing, China, [4]Georgetown University Medical Center, Washington, DC, USA, [5]Centre Hospitalier Régional d'Orléans, Orléans, France, [6]Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, Sevilla, Spain, [7]Praxis am Ebertplatz, Cologne, Germany, [8]GlaxoSmithKline, Brentford, UK, [9]ViiV Healthcare, Research Triangle Park, NC, USA, [10]ViiV Healthcare, Brentford, UK*

**Background:** In the Week (W) 48 analysis of the randomized, controlled, Phase III SALSA study, switching to the 2-drug regimen DTG/3TC fixed-dose combination was non-inferior to continuing various current ART regimens (CAR) in virologically suppressed adults with HIV-1, with no confirmed virologic withdrawals and a good safety profile. Here we present metabolic health results (post hoc analysis) from SALSA at W48.

**Methods:** Adjusted mean change from baseline (BL) to W48 for weight; fasting lipids, glucose, and insulin; HOMA-IR; FIB-4; and HbA1c were compared between treatment groups using mixed-model repeated measures (MMRM) for the overall SALSA population and by BL TAF or TDF use. For metabolic syndrome, logistic regression model adjusting for relevant BL variables was used for comparison between treatment groups.

**Results:** At BL, TAF was used in 34% (83/246) of participants (pts) switching to DTG/3TC and 37% (91/247) continuing CAR. Overall, adjusted mean weight change from BL to W48 was 2.1 kg in the DTG/3TC group and 0.6 kg in the CAR group (treatment difference, 1.5; 95% CI, 0.7, 2.3; Table). Weight change was similar between treatment groups in pts with BL TAF use (DTG/3TC, 1.6 kg; CAR, 1.4 kg; treatment difference, 0.2; 95% CI, −1.2, 1.5) and was higher in pts with BL TDF use (DTG/3TC, 2.4 kg; CAR, 0.1 kg; treatment difference, 2.4; 95% CI, 1.2, 3.6). Proportion of pts with ≥10% weight gain from BL was similar between treatment groups in the BL TAF subgroup and higher with DTG/3TC vs CAR in the BL TDF subgroup. Minimal changes in lipid parameters were observed in the overall and subgroup analyses. No treatment differences in prevalence of metabolic syndrome were observed in the overall (DTG vs CAR: OR [95% CI], 1.4 [0.6, 3.0]) and subgroup analyses (DTG vs CAR: BL TAF, 1.6 [0.5, 5.3]; BL TDF, 1.5 [0.4, 5.4]). Adjusted mean percent change from BL to W48 in fasting glucose and insulin, HOMA-IR, FIB-4, and HbA1c was generally similar between treatment groups in the overall and subgroup analyses.

**Conclusion:** At W48, differences in weight change from BL after switching to DTG/3TC were apparent among pts switching from TDF-containing regimens but not among pts switching from TAF-containing regimens. Although weight differed by BL NRTI, changes in other metabolic health parameters were similar between treatment groups in the overall and subgroup analyses. Comprehensive evaluation of metabolic outcomes remains important for management of people with HIV.

**Table.** Summary of Metabolic Health Outcomes at Week 48 of the SALSA Study, Overall and by Baseline TAF or TDF Use

| | Overall | | TAF subgroup | | TDF subgroup | |
|---|---|---|---|---|---|---|
| Parameters | DTG/3TC (N=246) | CAR (N=247) | DTG/3TC (N=83) | CAR (N=91) | DTG/3TC (N=108) | CAR (N=106) |
| Adjusted mean change from baseline in weight, kg (95% CI)[a] | 2.1 (1.5, 2.7) | 0.6 (0.1, 1.1) | 1.6 (0.5, 2.6) | 1.4 (0.6, 2.2) | 2.4 (1.5, 3.4) | 0.1 (−0.7, 0.8) |
| ≥10% weight gain from baseline, n/N (%) | 27/230 (12) | 9/224 (4) | 6/79 (8) | 6/86 (7) | 14/98 (14) | 3/95 (3) |
| Adjusted mean change from baseline in TC:HDL-C ratio, % (95% CI) | 1.8 (−0.8, 4.4) | 0.3 (−2.2, 2.9) | 1.7 (−2.9, 6.4) | −0.4 (−4.4, 3.6) | 3.9 (0.0, 8.0) | −0.7 (−4.3, 3.0) |
| Adjusted mean change from baseline in fasting glucose, % (95% CI)[b] | −0.6 (−1.8, 0.7) | 0.3 (−1.1, 1.8) | −2.6 (−4.7, −0.4) | −1.8 (−4.1, 0.5) | 0.7 (−1.2, 2.7) | 1.8 (−0.4, 4.1) |
| Adjusted mean change from baseline in fasting insulin, % (95% CI)[b] | 8.0 (1.2, 15.3) | 2.9 (−3.5, 9.8) | 11.1 (−0.8, 24.4) | −2.7 (−12.6, 8.4) | 7.5 (−2.5, 18.4) | 3.9 (−5.7, 14.4) |
| Adjusted mean change from baseline in HOMA-IR, % (95% CI)[b] | 6.8 (−0.7, 14.8) | 2.6 (−4.9, 10.8) | 6.3 (−6.1, 20.4) | −6.8 (−17.6, 5.5) | 9.9 (−1.4, 22.4) | 7.2 (−4.8, 20.8) |
| Adjusted mean change from baseline in FIB-4, % (95% CI)[c] | 0.6 (−2.3, 3.5) | 2.2 (−1.0, 5.5) | −0.5 (−5.4, 4.5) | 1.7 (−3.4, 7.0) | 1.1 (−3.2, 5.7) | 4.9 (−0.1, 10.2) |
| Adjusted mean change from baseline in $HbA_{1c}$, % (95% CI)[d] | 0.6 (−0.2, 1.4) | −0.4 (−1.1, 0.2) | −0.5 (−1.8, 0.9) | −1.4 (−2.5, −0.4) | 1.1 (−0.1, 2.3) | 0.3 (−0.7, 1.2) |

All adjusted analyses are calculated as estimated mean change (weight) or $\log_e$-transformed data (TC:HDL-C ratio, fasting glucose, fasting insulin, HOMA-IR, FIB-4, $HbA_{1c}$) from MMRM adjusting for baseline value (or $\log_e$-transformed baseline value), treatment, visit, baseline third agent class, CD4+ cell count, age, sex, race, treatment*visit interaction, and baseline value*visit interaction (or $\log_e$-transformed baseline value*visit interaction), with visit as the repeated factor. All subgroup analyses also adjusted for subgroup and treatment*subgroup, subgroup*visit, and subgroup*treatment*visit interactions.
[a]MMRM model also adjusted for prior TDF/EFV. [b]MMRM model also adjusted for baseline BMI and baseline hypertension. [c]MMRM model also adjusted for baseline BMI and baseline hepatitis C. [d]MMRM model also adjusted for baseline BMI, presence of hypertension, and presence of diabetes mellitus.

## 604 AGE AND OBESITY AS RISK FACTORS FOR DIABETES IN AFRICANS WITH HIV

**Lisa Hamzah**[1], Amelia Oliveira[2], Claire Norcross[2], Zoe Ottaway[3], Julie Fox[4], Burns Fiona[5], Andrew Ustianowski[6], Sarah L. Pett[5], Sarah Schoeman[7], Amanda Clarke[8], Caroline Sabin[5], Louise Goff[4], Frank A. Post[3], Cheryl Winkler[9]

*[1]St George's Hospital, London, UK, [2]King's College Hospital, London, UK, [3]King's College Hospital NHS Foundation Trust, London, UK, [4]King's College London, London,*

*UK, [5]University College London, London, UK, [6]University of Manchester, Manchester, England, [7]Leeds Teaching Hospitals NHS Trust, Leeds, UK, [8]Brighton and Sussex University Hospitals NHS Trust, Brighton, UK, [9]National Cancer Institute, Frederick, MD, USA*

**Background:** Diabetes mellitus (DM) is an important comorbidity in an ageing population. Age, male sex, and obesity are risk factors for DM, and obesity is particularly common in people of African ancestry. We explored the associations between obesity, age and DM in the GEN-AFRICA cohort comprising African people with HIV in the United Kingdom.

**Methods:** Cross sectional study of African women and men with HIV aged >18 years who were enrolled between May 2018 and February 2020. BMI was classified as normal (18.5-24.9), pre-obese (25-29.9), or obese (>30 kg/$m_2$). Associations between demographic factors including age (<40, 40-50, >50 years), HIV parameters (AIDS, time since diagnosis, use of ART, nadir/current CD4, HIV viral load), obesity (BMI >30 kg/$m_2$), hypertension and DM (clinical diagnoses), and kidney disease (eGFR and proteinuria) were evaluated using logistic regression. Variables with p<0.1 in univariable analysis were included in multivariable models. Models were a priori stratified by gender.

**Results:** A total of 2308 participants were included (mean age 48.0 [SD 9.9] years, 63% female, 99% on ART, median CD4 cell count 556 [IQR 409-721]/µL, 94% VL <200 c/mL); 36% were pre-obese and 44% obese, and 9.4% had DM (99% Type 2). Obesity was more common (52% vs. 31%, p<0.001) in female participants while DM was more prevalent (7.4% vs. 12.8%, p<0.001) in male participants; the prevalence of obesity and DM increased with age in both sexes (p<0.001). In univariable analysis, DM was associated with obesity as well as age (and hypertension, renal impairment, and proteinuria) in both female and male participants. After adjustment, age remained associated with DM whereas the association between obesity and DM was no longer significant (Table). Similar results were obtained when BMI was analysed in three strata, with normal BMI as referent (adjusted odds ratio 1.53 [0.74-3.18] for obese female, and 1.62 [0.90-2.90] for obese male participants).

**Conclusion:** Obesity is highly prevalent in this cohort of African people with well controlled HIV. The association between obesity and DM was attenuated in the multivariable models and no longer statistically significant. In both female and male participants, age >50 years was the strongest predictor of DM, and this group should be regularly screened for DM. Measures of central adiposity may be more useful predictors of DM in this population, especially in African women with HIV.

Table: Association with diabetes mellitus

| Exposure | FEMALE | | | | MALE | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable | | Multivariable | | Univariable | | Multivariable | |
| | OR [95% CI] | P value | OR [95% CI] | P value | OR [95% CI] | P value | OR [95% CI] | P value |
| Obesity | 1.59 [1.05, 2.39] | 0.02 | 1.19 [0.76, 1.85] | 0.44 | 1.91 [1.27, 2.29] | 0.002 | 1.40 [0.89, 2.20] | 0.14 |
| Age in years | | 0.0001 | | 0.001 | | <0.001 | | 0.01 |
| <40 | 1 | | 1 | | 1 | | 1 | |
| 40-50 | 4.56 [1.37, 15.2] | | 3.44 [0.99, 11.9] | | 12.3 [2.00, 117.0] | | 10.4 [1.38, 78.2] | |
| >50 | 15.6 [4.76, 51.5] | | 8.18 [2.30, 29.2] | | 29.5 [3.87, 224.4] | | 16.5 [2.24, 121.0] | |
| Current CD4 | 1.40 [1.00, 1.95] | 0.05 | 1.52 [0.84, 2.77] | 0.17 | 0.98 [0.71, 1.36] | 0.93 | | |
| Hepatitis B | 1.61 [0.75, 2.97] | 0.75 | | | 1.69 [0.92, 3.09] | 0.08 | 1.80 [0.94, 3.48] | 0.08 |
| Hypertension | 4.57 [3.01, 6.92] | <0.001 | 2.49 [1.57, 3.95] | <0.001 | 3.97 [2.57, 6.11] | <0.001 | 2.26 [1.41, 3.60] | 0.001 |
| Renal impairment | 5.29 [2.68, 10.4] | <0.001 | 2.46 [1.21, 4.99] | 0.012 | 2.35 [1.18, 4.68] | 0.01 | 0.75 [0.35, 1.63] | 0.48 |
| Proteinuria | 1.60 [1.03, 2.48] | 0.034 | 1.18 [0.73, 1.90] | 0.50 | 3.84 [2.49, 5.91] | <0.001 | 3.02 [1.88, 4.76] | <0.001 |

Hepatitis B = HBV surface antigen positive; renal impairment = estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m²; proteinuria = urine protein/creatinine ratio (uPCR) >15 mg/mmol.

## 605 CO-OCCURRING OBESITY & HIV ARE NOT ASSOCIATED WITH DIABETES MELLITUS IN SOUTH AFRICA

**Itai M. Magodoro**[1], Mongiwethu N. Dungeni[2], Alison C. Castle[3], Shakespear Mureyani[4], Mark J. Siedner[5]

*[1]University of Cape Town, Cape Town, South Africa, [2]Cavendish University Zambia, Lusaka, Zimbabwe, [3]Harvard TH Chan School of Public Health, Boston, MA, USA, [4]Gweru District Hospital, Gweru, Zimbabwe, [5]Africa Health Research Institute, Mtubatuba, South Africa*

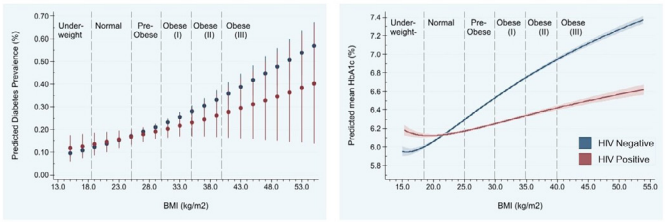
**Background:** Obesity and antiretrovirally treated (ART) HIV infection have been associated with increased insulin resistance, disordered beta-cell function and adipose tissue inflammation. Their co-occurrence is hypothesized to disproportionately increase the risk of diabetes mellitus (DM) among persons living with HIV (PWH) in high-income countries (HICs). This phenomenon, however, is less well established in low- and middle-income countries. We used a nationally-representative South African adult (≥15 years old) cross-sectional sample to investigate whether obesity among PWH, versus the general population, is associated with increased DM risk.

**Methods:** We analyzed individual-level data among 6,342 adults who participated in the 2016 South African Demographic Health Survey. Associations between prevalent DM, HbA1c and body mass index (BMI) stratified by HIV status were assessed by regression models and postestimation margins with adjustment for potential sociodemographic confounders, including age, sex and race.

**Results:** Population median [IQR] age was 35.0 [24.6-53.7] years with 18.9% HIV prevalence. Compared to HIV- controls, PWH were more frequently Black [98.2 vs. 81.8%], female [67.7 vs. 51.2%] and living in poverty (measured by multidimensional deprivation) [8.9 vs. 5.9%; all p<0.001]. Mean BMI [26.7 vs. 27.1 kg/$m_2$; p=0.27], and multivariable adjusted prevalence of overweight [BMI 25-30: 26.0 vs. 24.3%] and obesity class I [BMI 30-35: 15.7 vs. 14.6%], class II [BMI 35-40: 7.6 vs. 7.1%] and III [BMI>40: 6.7 vs. 6.6%] were similar between PWH and HIV- persons (all p>0.73. DM prevalence was also similar between the two groups [18.6 vs. 20.4%; p=0.30]. Increasing BMI was associated with increasing prevalence of DM, with similar relationships by HIV serostatus (Figure 1a). By contrast, HIV- individuals had higher predicted increases in HbA1c with increasing BMI > 25 (Figure 1b).

**Conclusion:** In a large population-representative sample in South Africa, obesity was highly prevalent and equally common among PWH and the general population. In contrast to reports from HIC settings, we found that obesity in South Africa may be correlated with a better glycemic profile among PWH than those without HIV. Regional differences in behaviors and genetics should be further explored to elucidate relationships between HIV and metabolic disease

**Fig 1. Predicted* (a) mean HbA1c and (b) DM prevalence stratified by HIV status.**




*Adjusted for age, sex, race, smoking status, rural/urban residence and multi dimensional deprivation.

## 606 FEMINIZING HORMONAL THERAPIES WORSEN CARDIOMETABOLIC PROFILES IN TRANSGENDER WOMEN

**Jordan Lake[1],** Han Feng[1], Hongyu Miao[1], Paula Debroy[1], Katherine McGowan[2], Sabina Haberlen[2], Wendy Post[3], Shalender Bhasin[4], Matthew Budoff[5], Todd Brown[3]

*[1]University of Texas at Houston, Houston, TX, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [4]Harvard Medical School, Boston, MA, USA, [5]Harbor–University of California Los Angeles Medical Center, Torrance, CA, USA*

**Background:** Cardiometabolic disease burden in transgender women (TW) is affected by feminizing hormonal therapies (FHT), HIV and antiretroviral therapy (ART), but little data are available with contemporary FHT regimens and well-matched controls. We assessed relationships between sex hormone concentrations, body composition and inflammatory biomarkers among TW and matched cisgender men (CM).

**Methods:** Adult TW on FHT (n=33) were recruited from Houston, TX and Baltimore, MD for a cross-sectional study (2018-2020). CM (n=60) from the Multicenter AIDS Cohort Study Cardiovascular 2 or 3 sub-studies were matched (2:1) to TW on HIV serostatus, age within 5 years, race/ethnicity, BMI category and ART type. All HIV+ persons had HIV-1 RNA <50 copies/ml on ART. Body composition was measured by non-contrast computed tomography. Sex hormones and inflammatory biomarker concentrations were measured centrally.

**Results:** TW were 71% non-white, 76% HIV+ (72% InSTI-based ART use) and had median age 51 years and BMI 29 kg/$m_2$. Only 31% of TW had testosterone suppression, with median total testosterone 325 vs 441 ng/dl for CM and similar free testosterone (3%). Median estradiol for TW was 85 vs 23 pg/ml for CM. TW had greater subcutaneous thigh muscle fat (16 vs 7 cm2, p<0.001) and tended to have greater subcutaneous abdominal fat (345 vs 279 cm2, p=0.09). TW had significantly (p<0.05) higher endothelin (ET)-1 (3.1 vs 1.5 pg/mL), EN-RAGE (23.0 vs 9.1 pg/ml) and adiponectin (5.6 vs 3.9 µg/ml) concentrations vs CM. Higher estradiol (r=0.374, p<0.001) and lower total testosterone (r=-0.30, p=0.006) concentrations correlated with greater thigh muscle fat; lower total testosterone concentrations also correlated with greater abdominal subcutaneous (r=-0.29, p=0.008) and visceral fat (r=-0.22, p=0.04) area. Higher estradiol concentrations correlated with higher adiponectin (r=0.24, p= 0.03), ET-1 (r=0.22, p= 0.046), and EN-RAGE (r=0.40, p<0.001) concentrations.

**Conclusion:** In this group of older TW on FHT, higher estradiol and lower total testosterone concentrations were associated with worse body composition and mixed effects on select cardiometabolic biomarkers. Specifically, greater visceral fat and fatty muscle infiltration and higher endothelin-1 and EN-RAGE concentrations have been associated with increased cardiovascular risk in the general population, though higher adiponectin is generally thought to be beneficial. More nuanced understanding of the relationships between FHT and cardiometabolic risk in TW is needed.

## 607 PROTEINURIA IS COMMON AMONG PEOPLE WITH HIV WITH CONTROLLED HIV VIREMIA

**Edgar T. Overton**[1], Amy Kantor[2], Kathleen Fitch[3], Paul M. Muntner[1], Mosepele Mosepele[4], Judith A. Aberg[5], Carl J. Fichtenbaum[6], Grace A. McComsey[7], Carlos Malvestutto[8], Michael T. Lu[9], Pamela S. Douglas[10], Steven Grinspoon[3], Heather J. Ribaudo[2], Christina Wyatt[10]

*[1]University of Alabama at Birmingham, Birmingham, AL, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]University of Botswana, Gaborone, Botswana, [5]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [6]University of Cincinnati, Cincinnati, OH, USA, [7]Case Western Reserve University, Cleveland, OH, USA, [8]The Ohio State University, Columbus, OH, USA, [9]Harvard Medical School, Boston, MA, USA, [10]Duke Clinical Research Institute, Durham, NC, USA*

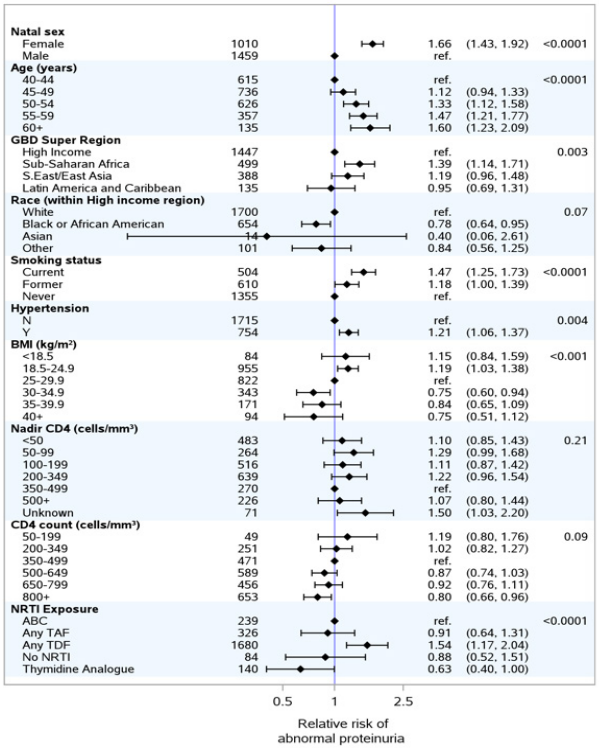
**Background:** HIV infection remains an established risk factor for chronic kidney disease (CKD). Increased urinary protein and albumin excretion assessment are important markers of CKD prevalence and progression. Here, we present data regarding prevalence of proteinuria and albuminuria among REPRIEVE participants with baseline urine testing.

**Methods:** REPRIEVE is an international primary cardiovascular prevention RCT of pitavastatin calcium vs. placebo among 7,770 PWH ages 40-75 on antiretroviral therapy with eGFR ≥60 mL/min/1.73mm$_2$. A representative subset of 2512 participants had urine collected at study entry. Previously defined categories of urine protein to creatinine ratios (uPCR) and albumin to creatinine ratios (uACR) were used. uPCR: Normal (<150mg/g), Moderately Increased (150-500mg/g), and Severely Increased (>500mg/g); uACR: Normal (<30mg/g), Moderately Increased (30-300mg/g), and Severely Increased (>300mg/g). These were dichotomized to Normal or Abnormal for log-binomial regression analysis. Risk of abnormal proteinuria and albuminuria was assessed by demographic, cardiometabolic, and HIV-specific data.

**Results:** Sample demographics (n=2512) included median age 49 years, 41% female sex, 47% black or African American race, median BMI 26 kg/m$_2$, median CD4 count 619 c/mm$_3$, and 98% with HIV VL <400cp/ml. Median eGFR was 98 mL/min/1.73mm$_2$; 36% had eGFR <90 mL/min/1.73mm$_2$. For uPCR (n=2475), 72% had normal, 25% moderately increased, and 3% severely increased values. For uACR (n=2512), 90% had normal, 9% moderately increased, and 1% severely increased values. In the adjusted model for abnormal proteinuria, female sex, older age, residence in sub-Saharan Africa, current or former smoking status, diagnosis of HTN, lower BMI and, use of TDF were associated with abnormal values. In the adjusted model for abnormal albuminuria, diagnosis of HTN, and certain NRTI exposures were associated with abnormal values. Neither nadir nor current CD4 count was associated with abnormal proteinuria or albuminuria.

**Conclusion:** In this cohort with controlled HIV, high CD4 cell counts, and preserved eGFR, abnormal proteinuria and albuminuria remain common (28% and 10%). While HIV parameters were not associated with abnormal values, TDF use was strongly associated with abnormal proteinuria. Additionally, certain modifiable comorbidities, including HTN and smoking, were associated with abnormal values. In PWH with preserved eGFR, subclinical kidney disease can be identified using urine measures.

**Figure: Relative Risk of Abnormal Proteinuria (uPCR ≥150mg/g)**




## 608 APOL1 VARIANTS, SICKLE CELL TRAIT, AND KIDNEY FAILURE IN AFRICANS WITH HIV

**Frank A. Post**[1], Rachel K. Hung[2], Julie Fox[2], Burns Fiona[3], Andrew Ustianowski[4], Lisa Hamzah[5], Sarah Schoeman[6], Amanda Clarke[7], Caroline Sabin[3], Cheryl Winkler[8]

*[1]King's College Hospital NHS Foundation Trust, London, UK, [2]King's College London, London, UK, [3]University College London, London, UK, [4]University of Manchester, Manchester, England, [5]St George's Hospital, London, UK, [6]Leeds Teaching Hospitals NHS Trust, Leeds, UK, [7]Brighton and Sussex University Hospitals NHS Trust, Brighton, UK, [8]National Cancer Institute, Frederick, MD, USA*

**Background:** Apolipoprotein L1 (APOL1) genetic variants and sickle cell trait (SCT) provide protection against trypanosomiasis and malaria respectively and have been associated with kidney disease in people of recent African ancestry. We analysed the relationship between APOL1 G1 and G2 variants, SCT and kidney disease in people of sub-Saharan African and Caribbean ancestry with HIV in the United Kingdom and report the population attributable fraction (PAF) for each exposure.

**Methods:** We conducted a cross-sectional study of HIV and co-morbid status and evaluated kidney function (creatinine-based estimated glomerular filtration rate [eGFR] and albuminuria). Exposures were APOL1 renal-risk genotypes (G1/G1, G1/G2 or G2/G2) and SCT (hemoglobin AS); the primary outcome was end-stage kidney disease (ESKD; eGFR <15 ml/min/1.73m$_2$, chronic dialysis, or kidney transplant); secondary outcomes were renal impairment (eGFR <60 mL/min/1.73m$_2$) and albuminuria (albumin/creatinine ratio >3 mg/mmol). Multivariable logistic regression was used to describe associations between APOL1 renal-risk genotypes/SCT and kidney disease outcomes, with adjustment for demographic, HIV and renal risk factors.

**Results:** We studied 2,895 individuals (mean age 48.1 [SD 10.3]; 57.2% female; median CD4 count 560 [IQR 401-733]; 93.1% HIV VL <200 c/mL); 354 (12.4%) had APOL1 renal-risk genotypes, 335 (11.6%) had SCT, and 99 (3.5%) had ESKD. APOL1 renal-risk genotypes and SCT were associated (adjusted odds ratio [95%CI]) with ESKD (10.9 [6.6-18.1] and 1.9 [1.0-3.5]), renal impairment (6.6 [4.6-9.5] and 1.8 [1.2-2.8]) and albuminuria (1.9 [1.4-2.6] and 1.5 [1.1-2.0]), respectively. No association between a single APOL1 risk variant (G1/G0 or G2/G0) and ESKD or renal impairment was observed. The PAF of ESKD was 49.4% for APOL1 renal-risk genotypes and 10.7% for SCT.

**Conclusion:** APOL1 renal-risk genotypes and SCT are predictors of kidney disease in people of African ancestry with well controlled HIV. Over half of ESKD in this population was attributable to these genetic variants. Novel

therapies, especially those targeting the APOL1 pathway, have the potential to substantially reduce the burden of ESKD in people of African ancestry with HIV, and their evaluation in this population should be prioritized.

| | N | Univariable | | | Multivariable* | | |
|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | p value | OR | 95% CI | p value |
| **End-stage kidney disease** | | | | | | | |
| *APOL1* renal risk genotypes | 99 | 10.31 | 6.81-15.60 | <0.001 | 10.58 | 6.22-17.99 | <0.001 |
| Sickle cell trait | 105 | 1.79 | 1.08-2.99 | 0.03 | 1.89 | 1.03-3.48 | 0.04 |
| **eGFR <60 mL/min/1.73m²** | | | | | | | |
| *APOL1* renal risk genotypes | 221 | 5.65 | 4.19-7.61 | <0.001 | 5.50 | 3.81-7.95 | <0.001 |
| Sickle cell trait | 237 | 1.67 | 1.16-2.41 | 0.006 | 1.81 | 1.18-2.78 | 0.007 |
| **uACR >3 mg/mmol** | | | | | | | |
| *APOL1* renal risk genotypes | 474 | 1.70 | 1.28-2.26 | <0.001 | 1.97 | 1.46-2.66 | <0.001 |
| Sickle cell trait | 496 | 1.54 | 1.16-2.05 | 0.003 | 1.48 | 1.08-2.03 | 0.01 |

*Adjusted for age, sex, region of ancestry, time since HIV diagnosis, prior AIDS, recent CD4 cell count, anti-HCV, diabetes, and cardiovascular disease; SCT models are additionally adjusted for *APOL1* renal risk status.

## 609 PETRAM RESULTS: BONE TURNOVER CHANGES ON 18F-PET/CT AFTER A RANDOMIZED SWITCH TO TAF

**Amelia E. Moore**[1], James E. Burns[2], Deidre Sally[2], Ana Milinkovic[2], Georgios Krokos[1], Joemon John[1], Christopher Rookyard[1], Erica Pool[2], Richard Gilson[2], Alejandro Arenas-Pinto[2], Gary Cook[1], David Dunn[2], Glen Blake[1], Sarah L. Pett[2]
*[1]King's College London, London, UK, [2]University College London, London, UK*

**Background:** The mechanism of bone loss in antiretroviral-treated HIV-positive patients is poorly understood. Plasma bone turnover markers(BTMs) suggest uncoupling of bone resorption and formation by a treatment effect on bone cells. Switching away from TDF to TAF-containing regimens has been associated with bone mineral density(BMD) gains measured by dual-energy X-ray absorptiometry (DXA). One explanation is reversal of ongoing subclinical bone loss in the TDF to TAF switchers. Quantitative imaging with 18F-PET/CT allows assessment of regional bone formation at specific skeletal sites and can help differentiate if BMD changes are associated with increased bone formation or reduced bone loss.

**Methods:** PETRAM, an open-label, randomised study conducted at a single UK site, enrolled non-osteoporotic virologically suppressed HIV-positive males, on >24 weeks rilpivirine/emtricitabine/TDF (RPV/FTC/TDF). They were randomised 1:1 to remain on RPV/FTC/TDF or switch to RPV/FTC/TAF. The protocol specified scanning by DXA (to measure BMD) and 18F-PET/CT at several regions of interest – with primary focus on the lumbar spine (LS) and total hip (TH) – at baseline, 24 weeks, and 48 weeks. However, the timing of scans was disrupted, and in some cases considerably delayed, by COVID-19. The primary analysis was therefore based on change between the baseline and final scans, adjusting for the interval between them. Regions of interest were drawn on the PET/CT images and the standardised uptake value (SUV) measured. A sample of 30 (15 per arm) was estimated to provide 90% power to detect a difference in change of 25% in SUV between the randomised groups.
**Results:** 32 males, median age 51 years, 76% White ethnicity, median duration RPV/FTC/TDF of 49 months, BMI 25.5 kg/m$_2$ were enrolled; 27(16 TAF:11 TDF) were included in the final analysis. The interval between baseline and final scans ranged between 23-103 weeks (median 55 weeks). There was no significant difference in change in SUV(18F-PET/CT) at the LS or TH between the TAF and TDF arms (Table); there was a trend towards improved LS BMD, but not TH BMD, in the TAF arm.
**Conclusion:** As measured by 18F-PET/CT, regional bone formation at the hip or LS in patients replacing TDF with TAF in their ART combination did not differ, and contrary to our hypothesis, switching to TAF vs. remaining on TDF over 23-103 weeks did not change BMD or SUV at these key skeletal sites. The improved LS BMD in those switching to TAF is consistent with findings from other TAF-switch studies.

**Table. PETRAM end-of-study 18F-PET/CT and DXA lumbar spine and total hip results**

| Parameter | Mean % change (95 % CI) | | Relative % difference: TAF vs. TDF (95% CI)* | P-value |
|---|---|---|---|---|
| | RPV/FTC/**TAF** | RPV/FTC/**TDF** | | |
| Lumbar Spine BMD (DXA) | +2.2 (1.0, 3.5) | -0.1 (-2.0, 1.9) | +2.0 (0.0, 4.0) | 0.05 |
| Lumbar Spine SUV (18F-PET/CT) | -8.4 (-13.7, -2.9) | -3.9 (-13.5, 6.8) | -2.8 (-12.0, 6.5) | 0.56 |
| Total Hip BMD (DXA) | -0.1 (-0.9, 0.6) | -0.2 (-1.4, 1.0) | 0.0 (-1.3, 1.4) | 0.94 |
| Total Hip SUV (18F-PET/CT) | -0.4 (-14.5, 15.9) | +0.3 (-13.8, 16.7) | -2.6 (-19.5, 14.3) | 0.77 |

*adjusting for baseline value and interval between first and last scan

## 610 ROSUVASTATIN WORSENS VITAMIN K2 STATUS WHICH IMPAIRS BENEFICIAL EFFECT ON BONE IN HIV

**Jared C. Durieux**[1], Sokratis N. Zisis[2], Christian F. Mouchati[2], Grace A. McComsey[2]
*[1]University Hospitals Cleveland Medical Center, Cleveland, OH, USA, [2]Case Western Reserve University, Cleveland, OH, USA*

**Background:** Vitamin K2 has shown a positive effect on bone health in the general population but has never been studied in HIV. We have previously shown in SATURN-HIV that rosuvastatin reduced immune activation in PLWH on antiretroviral treatment and improved hip BMD at 48 weeks however the effect on BMD was lost by 96 weeks. Due to laboratory data suggesting that statins impair vitamin K status, we investigated the effects of rosuvastatin on vitamin K status in SATURN-HIV as a mechanism for the lack of long-term effect on bone health.
**Methods:** We measured vitamin K-dependent dephosphorylated-uncarboxylated matrix Gla protein (MGP), a marker of K2 status (poor K2 status=high MGP), along with several bone formation markers including N-terminal propeptide of type-1 collagen (P1NP) and osteocalcin (OCN) in plasma samples from patients randomized to placebo (n=75) or active treatment (n=72; Rosuvastatin 10 mg daily) in the 96-week, SATURN-HIV clinical trial. Bone mineral density (BMD) measures of lumbar spine (L1-L4) and femoral neck were assessed by dual-energy absorptiometry. Constrained longitudinal analysis of covariance models were used to assess changes over time with random intercept to account for the dependency of repeated observations within the individual.
**Results:** Pretreatment, the overall median MGP was 519.25 ng/mL (IQR: 451.15, 593.33) and median P1NP was 54.27 ng/mL (IQR: 38.56, 67.95). In the active treatment group, there was a negative slope observed in femoral BMD and OCN and a positive slope in TNFαRII and spine BMD over the study period. There was not enough evidence (p>0.05) to suggest these changes were related to statin therapy. There was evidence of treatment effect on increases in MGP over 96 weeks (p=0.04) and decreases in P1NP to week 48 (p=0.04). In covariate adjusted models, increases in MGP was associated with decreases in femoral BMD, but not in P1NP, at week 96 (p=0.03).
**Conclusion:** Despite known benefits of statins in HIV, its effects on bone health are less clear. We provide evidence that Rosuvastatin increases MGP, signaling worse vitamin K2 status. Research is needed on whether supplementation with vitamin K2 may be warranted in the setting of statin therapy to avoid unfavorable effects on bone.

## 611 HIV-ASSOCIATED COPD IS CHARACTERIZED BY INCREASED SMALL AIRWAYS DYSFUNCTION ON CT

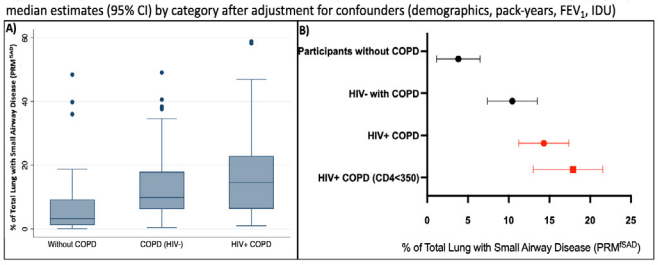
**Sarath Raju**[1], Andrew Gearhart[2], Nicole L. Brown[2], Michael B. Drummond[3], Robert Brown[1], Meredith McCormack[1], Gregory D. Kirk[1]
*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** HIV is associated with accelerated lung aging and Chronic Obstructive Pulmonary Disease (COPD). There remain gaps in our understanding of features unique to HIV-associated COPD and the HIV lung aging phenotype. The development of parametric response mapping (PRM) CT analysis, with joint analysis of inspiratory and expiratory CTs, allows for detection and quantification of small airways dysfunction that is associated with lung aging and was previously undetectable by conventional CT. Small airways dysfunction, is tied to greater respiratory morbidity, independent of lung function (FEV1). We aimed to leverage PRM to phenotype HIV-associated COPD and describe the burden of small airways dysfunction.
**Methods:** We utilized data from the Study of HIV in the Etiology of Lung Disease (SHIELD) COPD sub-study, which phenotypes COPD among PLWH and HIV-uninfected individuals with matched risk factors. Participants completed lung function and Chest CT evaluation. COPD was confirmed by post-bronchodilator spirometry. PRM was applied to CT images to quantify percentages of small airways disease (PRMfSAD) and emphysema (PRMemph). To describe small airways dysfunction in HIV-COPD, quantile regression models were generated, given highly skewed outcomes, with adjustment for relevant confounders, including demographics, FEV1, pack-years, and injection drug use.
**Results:** We studied 353 participants; 240 PLWH (68%) and 137 with COPD (39%). Among those with COPD, the majority had mild-moderate airflow obstruction (median FEV1% predicted 72[60-85]) and minimal emphysema (0.52%[0.12-2.03]). For those without COPD, there was no difference in PRMfSAD

by HIV. After adjusting for cofounders, including FEV1, greater PRMfSAD was observed in HIV+ COPD (median estimate 14.3%; 95%CI 11.2-17.4) than in HIV-uninfected participants with COPD (10.4%; 95%CI 7.38-13.5) (p=0.031). The highest PRMfSAD was observed in those with CD4+ counts<350 (17.3%; 95%CI 13.0-21.6) (Figure). In adjusted models, aside from HIV, age was the only factor associated with PRMfSAD. There was higher PRMemph in HIV+ COPD as well (p=0.046), though emphysema was minimal in the cohort.

**Conclusion:** HIV+ COPD is characterized by an increased burden of small airways dysfunction, even in a cohort with higher lung function. Our study suggests that PRM adds value in describing early lung aging in HIV. Longitudinal studies are now warranted to describe the long term impact, and drivers of, small airways dysfunction in HIV.

**Figure.** A) Depicts the distribution of functional small airways disease ($PRM_{fSAD}$) by HIV and COPD category B) Depicts median estimates (95% CI) by category after adjustment for confounders (demographics, pack-years, $FEV_1$, IDU)




## 612 HIV AND TB DRIVE NONCOMMUNICABLE LUNG DISEASE IN URBAN WEST AFRICA

New Investigator Scholar

**Douglas Fink**[1], David Oladele[2], Abigail L. Slack[1], Oluwatosin Odubela[2], Tomilola Musari-Martins[2], Adaobi Okechukwu[2], Kemi Adetayo[2], Sola Opaneye[2], Rufai Abubakar[2], Agatha David[2], Shumonta Quaderi[2], Marc Lipman[3], John Hurst[4], Oliver Ezechi[2]

*[1]London School of Hygiene & Tropical Medicine, London, UK, [2]Nigerian Institute of Medical Research, Lagos, Nigeria, [3]Royal Free Hospital, London, UK, [4]University College London, London, UK*

**Background:** There are very limited data describing burden of and risk factors for chronic lung disease (CLD) in people living with HIV (PLWH) in HIV high-prevalence settings. There is none comparing lung health and disease between PLWH and HIV-negative populations in west Africa. High-quality population-specific data are required to characterise disease burden and preventable causes of CLD to guide policy and improve health. In Lagos, Nigeria, this study aimed to report the prevalence of CLD, and quantify the contribution of risk factors including HIV infection.

**Methods:** A multi-centre cross-sectional observational study was conducted at three community clinics with individuals attending for routine follow-up. PLWH were recruited from the Nigerian Institute of Medical Research, Lagos, Nigeria. All HIV-negative participants received point-of-care HIV testing at the time of attendance. Subjects completed validated respiratory health questionnaires and performed spirometry lung function testing. Demographic information, medical history and a range of HIV outcomes were also recorded.

**Results:** Between January 2018 and October 2019 321 of those recruited (85.6%, 321/375) recorded acceptable spirometry. The prevalence of current tobacco smoking (11/321, 3.4%) and domestic biomass fuel exposure were low (6/321, 1.9%). Prior history of TB was significantly higher in PLWH (50/173, 28.9%) compared to HIV-negative participants (1/148, 0.7%). The median forced expiratory volume in the first second (FEV1) of PLWH was lower than in the HIV-negative comparator group (2.37L (IQR 2.07, 2.80) vs 2.73L (IQR 2.24, 3.36); p<0.0001), as was forced vital capacity (3.15L (IQR 2.69, 3.58) vs 3.38L (IQR 2.80, 4.12); p<0.0001). HIV exposure and previous tuberculosis (TB) were associated with airways obstruction across a range of reference spirometry values. HIV exposure was associated with increased odds of CLD once adjusted for age, sex, smoking history, BMI and previous TB (OR 2.25 (CI 1.26-4.03), p=0.006). Virological and immunological HIV outcomes (including most recent and nadir CD4 count and HIV viral load) did not associate with respiratory outcomes.

**Conclusion:** HIV exposure and previous TB represent risk factors for non-communicable CLD in urban west Africa in the absence of conventional risk factors, such as tobacco and biomass fuel. Population-level longitudinal studies are urgently required to define disease burden and guide interventions against preventable causes.

| | | HIV negative | | | | HIV positive | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Prevalence of bronchitis [n (%)] | Median FVC (IQR) | Median FEV1/FVC (IQR) | | Prevalence of bronchitis [n (%)] | Median FVC (IQR) | Median FEV1/FVC (IQR) |
| Total eligible [n (%)] | | 154 (98.1) | | | | 221 (84.5) | | | |
| Acceptable spirometry [n (%)] | Yes | 148 (96.1) | 2 (1.4) | 3.38 (2.80, 4.12) | 0.82 (0.77, 0.87) | 173 (78.3) | 10 (5.8) | 3.15 (2.69, 3.58) | 0.78 (0.72, 0.82) |
| Sex [n (%)] | Male | 76 (51.4) | 0 | 4.12 (3.61, 4.65) | 0.81 (0.76, 0.86) | 76 (43.9) | 6 (7.9) | 3.58 (3.25, 3.95) | 0.76 (0.71, 0.79) |
| | Female | 72 (48.7) | 2 (2.8) | 2.83 (2.54, 3.15) | 0.82 (0.79, 0.87) | 97 (56.1) | 4 (4.1) | 2.82 (2.51, 3.13) | 0.80 (0.74, 0.84) |
| Age [years] [n (%)] | ≤ 30 | 38 (24.3) | 1 (2.8) | 3.93 (3.21, 4.79) | 0.84 (0.79, 0.86) | 13 (7.6) | 1 (7.7) | 3.78 (3.13, 3.94) | 0.78 (0.72, 0.84) |
| | 31-40 | 53 (35.8) | 0 | 3.38 (2.82, 4.18) | 0.81 (0.78, 0.85) | 42 (24.6) | 2 (4.8) | 2.99 (2.69, 3.43) | 0.80 (0.76, 0.84) |
| | 41-50 | 43 (29.1) | 0 | 3.07 (2.58, 3.96) | 0.83 (0.77, 0.87) | 76 (44.4) | 6 (7.9) | 3.05 (2.57, 3.50) | 0.77 (0.73, 0.82) |
| | 51-60 | 18 (10.8) | 1 (6.3) | 3.14 (2.71, 3.56) | 0.79 (0.72, 0.87) | 30 (17.5) | 1 (3.3) | 3.40 (3.00, 3.69) | 0.76 (0.72, 0.80) |
| | >60 | 0 | 0 | - | - | 10 (5.9) | 0 | 3.27 (2.40, 3.50) | 0.73 (0.70, 0.83) |
| Body Mass Index [kg/m²] [n (%)] | <18.5 | 2 (1.4) | 0 | 3.80 (3.63, 3.96) | 0.79 (0.69, 0.90) | 11 (6.4) | 0 | 3.32 (3.02, 3.74) | 0.75 (0.69, 0.85) |
| | 18.5-23.9 | 45 (31.1) | 0 | 3.94 (3.20, 4.58) | 0.80 (0.76, 0.86) | 63 (36.4) | 3 (4.8) | 3.15 (2.80, 3.58) | 0.76 (0.72, 0.82) |
| | 24-29.9 | 60 (40.5) | 1 (1.7) | 3.31 (2.84, 3.87) | 0.82 (0.77, 0.87) | 67 (38.7) | 5 (7.5) | 3.18 (2.56, 3.69) | 0.79 (0.73, 0.82) |
| | ≥30 | 40 (27.0) | 1 (2.5) | 2.89 (2.58, 3.56) | 0.82 (0.79, 0.87) | 32 (18.5) | 2 (6.3) | 2.91 (2.54, 3.32) | 0.77 (0.73, 0.84) |
| Smoking status [n (%)] | Current | 8 (5.4) | 0 | 3.82 (2.92, 4.79) | 0.81 (0.80, 0.85) | 3 (1.7) | 0 | 2.98 (2.56, 3.39) | 0.78 (0.69, 0.79) |
| | Ex-smoker | 12 (8.1) | 0 | 4.38 (4.01, 4.68) | 0.78 (0.75, 0.83) | 38 (22.0) | 5 (13.2) | 3.65 (3.25, 3.87) | 0.76 (0.71, 0.79) |
| | Never | 128 (86.5) | 2 (1.6) | 3.26 (2.71, 3.95) | 0.82 (0.78, 0.87) | 132 (76.3) | 5 (3.8) | 3.06 (3.58, 4.24) | 0.78 (0.73, 0.82) |
| Previous diagnosis of asthma or chronic lung disease [n (%)] | Yes | 2 (1.4) | 2 (100) | 3.12 (2.85, 3.38) | 0.79 (0.77, 0.80) | 5 (2.9) | 0 | 3.64 (2.74, 3.68) | 0.74 (0.17, 0.76) |
| Previous TB diagnosis [n (%)] | Yes | 1 (0.7) | 0 | 4.20 | 0.78 | 50 (28.9) | 4 (8.0) | 3.32 (2.77, 3.67) | 0.76 (0.71, 0.80) |
| | No | 147 (99.3) | 2 (1.4) | 3.38 (2.77, 4.12) | 0.82 (0.77, 0.87) | 123 (71.1) | 6 (4.9) | 3.06 (2.63, 3.50) | 0.78 (0.74, 0.83) |
| Exposure to biomass fuel for cooking [n (%)] | Yes | 1 (0.7) | 0 | 2.52 | 0.82 | 5 (2.9) | 0 | 3.28 (2.53, 3.34) | 0.76 (0.72, 0.85) |
| Liquid petroleum gas primary cooking fuel [n (%)] | Yes | 117 (79.1) | 1 (0.9) | 3.38 (2.83, 4.12) | 0.82 (0.78, 0.87) | 112 (64.7) | 8 (7.1) | 3.19 (2.72, 3.65) | 0.78 (0.73, 0.82) |
| Kerosene primary cooking fuel [n (%)] | Yes | 15 (10.1) | 0 | 3.34 (2.52, 4.12) | 0.79 (0.76, 0.87) | 44 (25.4) | 1 (2.3) | 3.08 (2.79, 3.39) | 0.77 (0.72, 0.82) |
| Occupation [n (%)] | Manual | 31 (21.0) | 0 | 3.44 (2.53, 4.20) | 0.80 (0.76, 0.86) | 35 (20.4) | 1 (2.9) | 3.41 (2.82, 3.68) | 0.77 (0.74, 0.82) |
| | Non-manual | 105 (71.0) | 2 (1.9) | 3.26 (2.83, 4.09) | 0.82 (0.78, 0.87) | 119 (68.8) | 6 (5.0) | 3.07 (2.63, 3.49) | 0.78 (0.72, 0.82) |
| | Unemployed/ Retired | 12 (8.1) | 0 | 3.52 (2.77, 4.22) | 0.84 (0.79, 0.88) | 22 (10) | 3 (15.8) | 3.34 (2.53, 3.66) | 0.76 (0.70, 0.84) |

## 613 HIV INFECTION DOES NOT EXPLAIN HIGHER NICOTINE METABOLISM IN PEOPLE WITH HIV (PWH)

**Robert Gross**[1], Warren B. Bilker[1], Xiaoyan Han[1], Michael Plankey[2], Deanna Ware[2], Mackey Friedman[3], Gypsyamber D'Souza[4], Steven Wolinsky[5], Robert Schnoll[1], Rachel F. Tyndale[6], Rebecca L. Ashare[7]

*[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Georgetown University, Washington, DC, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]The Johns Hopkins University, Baltimore, MD, USA, [5]Northwestern University, Evanston, IL, USA, [6]University of Toronto, Toronto, Canada, [7]State University of New York at Buffalo, Buffalo, NY, USA*

**Background:** Cigarette smoking in PWH is 2-3x that of HIV uninfected people and PWH have lower quit rates per attempt. Our work demonstrated much higher nicotine metabolism, measured by the nicotine metabolite ratio (NMR; 3-hydroxy cotinine/cotinine), in PWH than HIV uninfected people. Higher NMR is associated with more difficulty quitting smoking. We hypothesized that HIV infection might upregulate the NMR.

**Methods:** We compared NMR from plasma pre- and post-HIV infection in cigarette smokers who seroconverted in the MACS cohort. Eligibility included having plasma stored prior to and after confirmed HIV infection and smoking cigarettes at both time points. Any antiretroviral therapy (ART) use was exclusionary. Cotinine and 3-hydroxycotinine were measured in stored plasma using liquid chromatography-tandem mass spectrometry. We used the Wilcoxon signed rank test to compare NMR pre- and post-HIV infection. We targeted a sample size of 71 pairs to have 80% power to detect a clinically meaningful 0.1 unit increase in NMR with a 5% type I error rate.

**Results:** We analyzed samples obtained between May 1984 and December 1993 in 78 men, median age 34.5 years (range: 24-53) who seroconverted with a median pre-HIV plasma cotinine of 267 ng/ml (range: 14- 649) and median post-HIV plasma cotinine of 252 ng/ml (15-267). The median NMR pre-HIV infection was 0.45 (IQR 0.32, 0.54) and post-HIV infection was 0.46 (IQR 0.34, 0.56) with a mean (post-pre within subject) difference of 0.01 increase (IQR 0.05 decrease, 0.09 increase), p=0.25. The largest changes were a decrease in NMR of 0.55 units and an increase of 0.23 units. There was no evidence of differences when analyses were stratified by: a) > or < 1 year between an individual's samples or b) HIV+ sample obtained > or < 180 days after HIV infection.

**Conclusion:** HIV acquisition had no measurable effect on NMR. Since prior work consistently showing higher NMR in PWH included only individuals on ART, these results suggest that upregulation of the NMR may be due to direct pharmacologic effects of ART or metabolic changes in response to HIV infection and its treatment over time. If follow-on studies show pharmacologic effects, changing the choice of ART to managing HIV infection in HIV+ smokers to decrease NMR may help increase quit rates.

## 614 PREVALENCE OF ANEMIA AND RISK FACTORS IN PEOPLE WITH HIV IN THE MODERN ART ERA

New Investigator Scholar

**Raynell Lang**[1], M. John Gill[2], Richard Moore[3], Michael J. Silverberg[4], Amy Justice[5], Amanda Willig[6], Angel Mayor[7], Marina B. Klein[8], Michael A. Horberg[9], Kelly Gebo[3], Ronald J. Bosch[10], Laura Bamford[11], Jennifer S. Lee[1], Keri N. Althoff[1]

*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]Southern Alberta Clinic, Calgary, Canada, [3]The Johns Hopkins University School of*

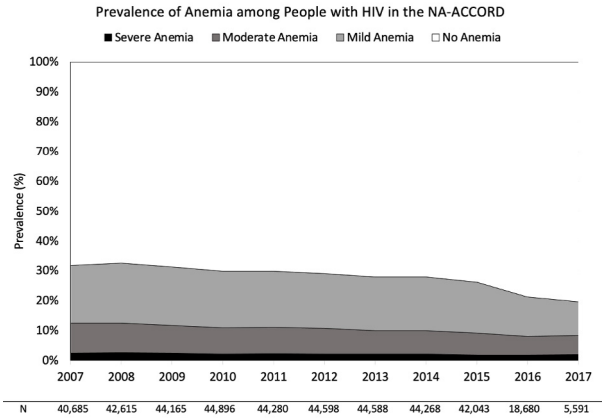
*Medicine, Baltimore, MD, USA, [4]Kaiser Permanente Division of Research, Oakland, CA, USA, [5]Yale School of Medicine & VA Connecticut Healthcare System, West Haven, CT, USA, [6]University of Alabama at Birmingham, Birmingham, AL, USA, [7]Universidad Central del Caribe, Bayamon, PR, USA, [8]McGill University Health Center, Montreal, Canada, [9]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [10]Harvard TH Chan School of Public Health, Boston, MA, USA, [11]University of California San Diego School of Medicine, La Jolla, CA, USA*

**Background:** In the modern ART era, anemia has become less common in people with HIV (PWH) however, its prevalence and risk factors remain largely unknown. As anemia is an independent predictor of increased morbidity and mortality in PWH, we aimed to estimate its prevalence and examine the clinical and laboratory associations with anemia.

**Methods:** Using the NA-ACCORD, we estimated the annual prevalence between 01/01/2007-12/31/2017 of mild (11.0-12.9g/dL men, 11.0-11.9g/dL women), moderate (8.0–10.9g/dL) and severe (<8.0g/dL) anemia in PWH. Poisson regression models with robust variance estimated crude and adjusted prevalence ratios (aPR) and 95% confidence intervals ([,]) comparing risk factors over time for those ever having a measure of moderate/severe anemia vs. no/mild anemia during the study period. Adjusted models included age, sex, race/ethnicity, HIV acquisition risk, BMI, diabetes, hypertension, high cholesterol, chronic kidney disease, statin use, AIDS diagnoses, Hepatitis C (HCV) and B infection at or prior to study entry. Low (≤200cells/$mm_3$) CD4 count and unsuppressed HIV RNA (>200 copies/mL) were time-varying in each calendar year; if there were multiple measurements in a given year, the median was used.

**Results:** Among 84,119 PWH, 41,964 (49.9%) had at least one measure of anemia with 20,379 (24.2%) having mild anemia, 14,936 (17.8%) moderate anemia and 6,649 (7.9%) severe anemia during follow-up. The majority was normocytic anemia (74.1%), however microcytic anemia increased from mild anemia (7.7%) to severe anemia (20.6%). The prevalence of mild anemia (19.3% to 11.3%, p for trend<0.001) and moderate anemia (9.8% to 6.4%, p for trend<0.001) decreased significantly, but severe anemia remained unchanged (2.6% to 2.1%, p for trend=0.422) (Figure 1). Compared with PWH with no/mild anemia, the adjusted prevalence of moderate/severe anemia was greater among those with low CD4 counts (aPR=2.97 [2.86, 3.09]) and unsuppressed HIV RNA (aPR=1.40 [1.35, 1.46]). ART use at hemoglobin measure was similar among both groups (~75%). Moderate/severe anemia was more prevalent among women, Non-Hispanic Black race (vs. Non-Hispanic White), with HCV and with a history of injection drug use (vs. MSM).

**Conclusion:** Despite decreasing over time, the prevalence of anemia among PWH is higher than that reported in the general population of high-income countries (~5%). The greatest burden of anemia in PWH was seen among those with low CD4 counts and high viral loads, emphasizing the importance of effective ART.




## 615 ASSOCIATION OF PHENOTYPIC AGING WITH COMORBIDITIES, FRAILTY, AND INFLAMMATORY MARKER

**Win Min Han**[1], Tanakorn Apornpong[1], Sivaporn Gatechompol[1], Sasiwimol Ubolyam[1], Stephen J. Kerr[1], Kristine Erlandson[2]

*[1]HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [2]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** People with HIV (PWH) suffer higher age-related comorbidities including frailty, neurocognitive impairment (NCI), and cardiometabolic diseases than people without HIV. Aging among PWH occurs heterogeneously, however some prior studies suggest that the aging process among PWH is faster than people without HIV.

**Methods:** A cross-sectional study was conducted among older PWH and age- and sex-matched HIV-negative controls to compare phenotypic age and phenotypic age acceleration (PAA) in older PWH and HIV-negative controls. Phenotypic age was calculated using chronological age and 9 biomarkers from complete blood counts, inflammatory, metabolic-, liver- and kidney-related parameters. PAA was calculated as the difference between chronological age and phenotypic age. Multivariate logistic regression models were used to identify the factors associated with higher PAA, defined as having higher than the median value. We assessed aging-related comorbidities including the Veterans Aging Cohort Study (VACS) index, frailty, NCI and inflammation (hsCRP and IL-6). Area under the receiver operating characteristics curve (AROC) was used to assess model discrimination for frailty.

**Results:** Between 2017 and 2018, 333 PWH and 102 HIV-negative controls (38% female) with median chronological age of 54 (IQR 52-59) and 55 (IQR 53-58) years, respectively, were enrolled. Median phenotypic age (49.4 vs. 48.5 years, p=0.54) and PAA (-6.7 vs. -7.5, p=0.24) were higher in PWH than the controls, although not statistically significant. PWH with higher PAA had lower CD4/CD8 ratio (0.88 [IQR 0.63-1.22] vs. 1.00 [IQR 0.74-1.33], p=0.03) and higher VACS index (22.2 [IQR 12-28] vs. 22.6 [IQR 18-34], p=0.01). In multivariate analysis including both PWH and uninfected controls, male sex (adjusted odds ratio=1.68 [95%CI=1.03-2.73]), current smoking (2.74 [1.30-5.79]), diabetes mellitus (2.97 [1.48-5.99]), hypertension (1.67 [1.02-2.72]), frailty (3.82 [1.33-10.93]), and higher IL-6 levels (1.09 [1.04-1.15]), but not HIV status and NCI, were independently associated with higher PAA. Phenotypic age discriminated frailty better than chronological age alone (AROC 0.76 [0.66-0.85] vs. 0.66 [0.55-0.77], p=0.04).

**Conclusion:** While PWH did not appear to have accelerated aging in our cohort, the phenotypic aging marker was significantly associated with systemic inflammation, frailty, and cardiovascular disease risk factors. This simple aging marker could be useful to identify high-risk PWH within the similar chronological age group.

## 616 L-FERRITIN AND TIM-1 ARE ASSOCIATED WITH FRAILTY MEASURES IN PEOPLE WITH HIV

**Harpreet Kaur**[1], Robert Kalayjian[2], Kunling Wu[3], Katherine Tassiopoulos[3], Frank Palella[4], Babafemi O. Taiwo[4], William Bush[5], Corrilynn O. Hileman[2], Roger Bedimo[6], Susan L. Koletar[7], Ronald J. Ellis[8], Kristine Erlandson[9], Asha R. Kallianpur[10]

*[1]Cleveland Clinic, Cleveland, OH, USA, [2]MetroHealth Medical Center and Case Western Reserve School of Medicine, Cleveland, OH, USA, [3]Harvard T. H. Chan School of Public Health, Boston, MA, USA, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [5]Case Western Reserve University, Cleveland, OH, USA, [6]VA North Texas Health Care System, Dallas, TX, USA, [7]The Ohio State University, Columbus, OH, USA, [8]University of California San Diego, San Diego, CA, USA, [9]University of Colorado-Anschutz Medical Campus, Aurora, CO, USA, [10]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA*

**Background:** People with HIV (PWH) are at high risk of physical-function impairment and frailty. Iron transport is key to energy production and is dysregulated by HIV and inflammation. We previously linked higher cerebrospinal fluid levels of the antioxidant iron transporter heavy-chain (H)-ferritin (Fth1) to better cognitive function in PWH. Here, we evaluated whether higher serum Fth1 and light-chain (L)-ferritin (Ftl), and lower urine T-cell immunoglobulin and mucin domain (Tim)-1 (Fth1 receptor) levels are associated with better frailty measures in PWH.

**Methods:** Serum Fth1, Ftl, inflammation markers (IL-6, TNFR2), and urine Tim-1 were quantified by ELISA (immunoassay) at entry in 324 PWH from the ACTG A5322 (HAILO: HIV Infection, Aging, and Immune Function Long-Term Observational) Study with frailty and cognitive assessments. Pre-frailty and frailty were assessed using the Fried criteria. Relationships at HAILO entry amongst biomarker levels, HIV clinical and demographic variables were tested using Pearson's chi-square test, non-parametric tests for trend, or Spearman's correlations. Multivariable linear or logistic regression models evaluated Fth1, Ftl, and Tim-1 associations with pre-frail/frail status and average 4-meter walk time and grip strength, adjusting for potential confounders, including cognitive function and inflammation, and stratifying by sex.

**Results:** Mean age was 52 years (19% females, median nadir CD4 212 cells/μL, 96% with plasma HIV RNA<200 copies/mL); 40% were pre-frail and 4% frail at entry. Serum Fth1 was correlated to Ftl (rho=0.14, p<0.01) but not to urine

Tim-1. In univariate analyses, Tim-1 was higher and Ftl lower across non-frail/pre-frail/frail groups (ptrend=0.06 and 0.02, respectively); higher Tim-1 was associated with pre-frailty (Odds Ratio (OR) 1.5, p<0.01) and combined pre-frailty/frailty (OR 2.3, p=0.01) vs. non-frail PWH. Higher Ftl was associated with faster 4-meter walk time (beta -0.045, p<0.01), lower odds of weak grip (OR 0.49, p<0.01), and less frailty, particularly in females (OR 0.28, p=0.03). Serum Fth1 was not associated with frailty measures. Multivariable-adjusted associations were similar and are shown below (Table).

**Conclusion:** Increased urine Tim-1 is a marker of risk for pre-frailty and frailty in PWH. Higher serum Ftl is associated with preserved motor function and less pre-frailty/frailty, particularly in females. Longitudinal analyses of frailty outcomes are underway. Further studies are needed to delineate causal pathways.

Multivariable Associations of Serum Ftl and Urine Tim-1 with Frailty and its Motor Components

| Biomarker (units=ng/mL) | (Pre-Frail+Frail) *vs.* non-Frail *Adj OR (95% CI)* | 4-Meter Walk Time (secs) *Beta or Adj OR* (95% CI) | Grip Strength (kg) *Beta or Adj OR* (95% CI) |
|---|---|---|---|
| ↑Ftl | All: Adj OR 0.82 (0.59, 1.1) | All: -0.033 (-0.064,-0.002)*<br>F: -0.087 (-0.148, -0.026 )** | All: 0.080 (0.019, 0.142)*<br>F: 0.230 (0.042, 0.418)* |
| ≥median *vs.* <median | All: Adj OR 0.56 (0.35, 0.92)*<br>F: Adj OR 0.29 (0.03, 0.98)*<br>M: Adj OR 0.63 (0.37, 1.1) | -- | ***Weak grip:***<br>All: Adj OR 0.50 (0.29, 0.88)*<br>F: Adj OR 0.24 (0.05, 1.1)<br>M: Adj OR 0.55 (0.30,1.0)* |
| Top *vs.* bottom quartile | -- | ***Slowness:***<br>F: Adj OR 0.06 (0.01, 0.61)*<br>M: Adj OR 0.78 (0.41, 1.5) | -- |
| ↑Tim-1 | All: Adj OR 1.4 (1.0, 1.9)* | All: 0.021 (-0.004, 0.046) | All: -0.027 (-0.067, 0.013) |
| Top *vs.* bottom quartile | All: Adj OR 2.6 (1.2, 5.5)* | ***Slowness:***<br>All: Adj OR 0.86 (0.40, 1.9)<br>F: Adj OR 6.5 (0.60, 70.0) | ***Weak grip:***<br>All: Adj OR 1.7 (0.68, 4.0)<br>F: Adj OR 0.48 (0.06, 3.8) |

*Adj OR*=adjusted odds ratio; *F*=females; *M*=males (gender identity information not available); *CI*=Confidence Interval. Models adjust for risk factors with univariate p≤0.10, including: age, sex, race/ethnicity, IL-6, TNFR2, anemia, comorbidity, and cognitive function. *p<0.05; **p<0.01

## 617 MUSCLE QUALITY AND PHYSICAL FUNCTION IN MEN WITH AND WITHOUT HIV

**Jing Sun**[1], Todd Brown[2], Susan Langan[1], Frank Palella[3], Jordan Lake[4], Lawrence A. Kingsley[5], Wendy Post[2], Kristine Erlandson[6]

*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3]Northwestern University, Chicago, IL, USA, [4]McGovern Medical School, Houston, TX, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** Data on muscle area and density and their impact on physical function over time among people with and without HIV (PWH and PWoH) are limited. We sought to assess associations of individual and aggregated abdominal and thigh muscle area and density with longitudinal physical function among PWH and PWoH using data from the Multicenter AIDS Cohort Study (MACS), a cohort of men who have sex with men.

**Methods:** Single-slice computed tomography scans were analyzed for left and right abdominal and thigh muscle (lateralis, rectus, psoas, paraspinal, quadriceps, and hamstring muscle) area and density for 798 men at index visit. Gait speed and grip strength were evaluated twice annually using standard methods from the index visit up to 5 years. Aggregated muscle quality was summarized using factor analysis. Using age as a time scale, we assessed the longitudinal association of gait speed and grip strength by muscle area and density using multivariable linear regression models with a generalized estimating equation.

**Results:** At index visit, 61% were HIV seropositive, median age was 54 years (IQR 49-59), 61% were white, 32% black, 10% Hispanic, 22% had BMI>30 $kg/m_2$, and 14% had diabetes. Compared to PWoH, PWH had higher muscle density (less fat) and area, except for rectus and psoas muscles. Older age, Black race, Hispanic ethnicity, diabetes, high total cholesterol, and low high-density lipoprotein were independently associated with slower gait speed; and Black race and Hispanic ethnicity with lower grip strength. All individual muscle quality was associated with gait speed and grip strength. Factor analysis generated 4 factors that represented 73.4% of the variance in all muscle quality (Table). Factor 1 represented all density measures and contributed the most to variance; factor 2 represented all area measures. Every unit increase in overall muscle density (factor 1) was independently associated with 0.03 meter/second (95% CI: 0.02, 0.04, p<0.01) faster gait speed. Overall muscle density (factor 1), overall muscle area (factor 2), and abdominal muscle area and density (factor 3 and 4) were each independently associated with grip strength (all p<0.01).

**Conclusion:** Low overall muscle density was associated with gait speed decline. Low overall muscle density and area, especially abdominal muscles, were associated with grip strength decline. These results highlight the importance of improving muscle quality to improve physical function among men aging with and without HIV.

**Table.** Results of exploratory factor analysis on muscle area and density with a four-factor solution in Multicenter AIDS Cohort (MACS)

| Muscle quality | | Factor Loadings | | | | Communality* |
|---|---|---|---|---|---|---|
| | | Factor1 | Factor2 | Factor3 | Factor4 | |
| Abdominal muscle area | Right Lateralis | -0.00173 | 0.79038 | 0.33343 | 0.14012 | 75.6 |
| | Left Lateralis | -0.00904 | 0.80887 | 0.31106 | 0.14123 | 77.1 |
| | Right Rectus | 0.34423 | 0.51861 | -0.39248 | 0.52267 | 81.5 |
| | Left Rectus | 0.27755 | 0.55254 | -0.41016 | 0.51196 | 81.3 |
| | Right Psoas | 0.25326 | 0.59407 | -0.48869 | -0.41539 | 82.8 |
| | Left Psoas | 0.25038 | 0.62424 | -0.47084 | -0.40284 | 83.6 |
| | Right Paraspinal | 0.17229 | 0.66561 | 0.57522 | 0.05070 | 80.6 |
| | Left Paraspinal | 0.16683 | 0.67856 | 0.56459 | 0.04339 | 80.9 |
| Thigh muscle area | Quadriceps | 0.24599 | 0.69311 | -0.16981 | -0.17142 | 59.9 |
| | Hamstring | 0.16735 | 0.60073 | -0.15155 | -0.19014 | 44.8 |
| Abdominal muscle density | Right Lateralis | 0.84357 | -0.28375 | 0.09668 | 0.05508 | 80.5 |
| | Left Lateralis | 0.83536 | -0.27448 | 0.10449 | 0.02557 | 78.5 |
| | Right Rectus | 0.71820 | -0.15192 | -0.17288 | 0.42286 | 74.8 |
| | Left Rectus | 0.73172 | -0.1553 | -0.16737 | 0.41785 | 76.2 |
| | Right Psoas | 0.79711 | -0.01562 | -0.08152 | -0.27508 | 71.8 |
| | Left Psoas | 0.80257 | -0.02281 | -0.08232 | -0.28200 | 73.1 |
| | Right Paraspinal | 0.80078 | -0.02675 | 0.29050 | -0.14994 | 74.9 |
| | Left Paraspinal | 0.81661 | -0.04481 | 0.28950 | -0.14847 | 77.4 |
| Thigh muscle lean density | Quadriceps | 0.68067 | -0.1974 | 0.09036 | 0.00763 | 51.0 |
| | Hamstring | 0.72718 | -0.29474 | 0.06342 | -0.07146 | 62.5 |
| Eigenvalues** | | 6.51 | 4.67 | 1.96 | 1.54 | |
| % of the total variance | | 32.5% | 23.4% | 9.8% | 7.7% | |
| Total Variance | | | | | 73.4% | |

*Communality is defined as the proportion of each muscle measurement's variance that can be explained by the retained factors. Variables with high values are well represented, variables with low values are not well represented.
**Eigenvalue is the variance of the factor; expect the first factor to account for the most variance.

## 618 THE FUNCFRAIL SCORE TO DISCRIMINATE FRAILTY IN OLDER ADULTS WITH HIV

**Matilde Sánchez-Conde**[1], Antonio Antela[2], Jorge Vergas[3], Margarita Ramírez[4], Pablo Ryan[5], Fernando Dronda[1], Maria José Galindo[6], Miguel Torralba[7], Maria Jesús Bustinduy[8], Alfonso Cabello Úbeda[9], Carmen Busca Arenzana[10], Isabel Machuca1[1], Fatima Brañas[5]

*[1]Hospital Ramón y Cajal, Madrid, Spain, [2]Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain, [3]Hospital Universitario Clínico San Carlos, Madrid, Spain, [4]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [5]Hospital Universitario Infanta Leonor, Madrid, Spain, [6]Hospital Clinic of Valencia, Valencia, Spain, [7]Hospital Universitario de Guadalajara, Guadalajara, Spain, [8]Hospital Donostia, San Sebastián, Spain, [9]Fundacion Jimenez Diaz, Madrid, Spain, [10]Hospital La Paz Institute for Health Research, Madrid, Spain, [11]Hospital Universitario Reina Sofia, Cordoba, Spain*

**Background:** The number of older adults with HIV is growing but data about this population are still scarce and mainly focused on comorbidity instead of on physical function and frailty. Frailty has a paramount importance because it has been related with worse clinical prognosis (morbidity, falls and death) but with a chance of success if detected. Different tools can be used to screen frailty but none of them have been developed specifically for the people with HIV. Our objective was to develop a screening tool to discriminate frailty in older adults with HIV in a simple way in the daily practice.

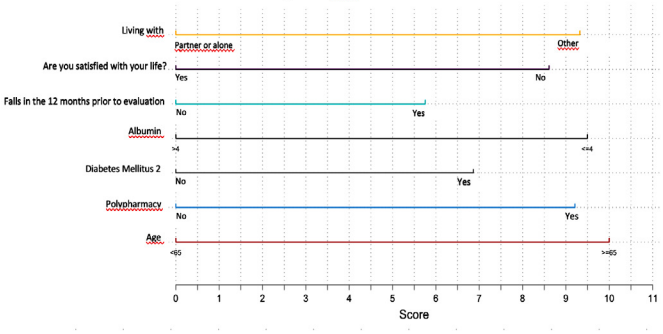
**Methods:** Prospective multicenter longitudinal cohort: the FUNCFRAIL Study. Patients 50 or over with HIV were included. We recorded sociodemographic data, HIV infection-related data, comorbidities, and frailty, defined according to Fried's criteria. Multivariate logistic regression model was performed for those variables found to be associated with frailty in the univariate analyses to determine which were independently associated with frailty to estimate the predictive score (FUNCFRAIL Score). Frailty was treated as a binary variable: frailty vs prefrailty/robust. Discrimination for frailty prediction was estimated using the area under the ROC curve.

**Results:** 798 patients were included. 24.7% were women, mean age was 58.2 (6.3) and 14.7% were 65 or over. Mean years with known HIV infection was 20.2 (9.1) and 90.3% were virologically controlled. Frailty prevalence was 5.6%. 38,3% patients had 3 or more comorbidities with a mean number of comorbidities of 2.2 (1.7). 13.5% had diabetes, 15.6% had at least one fall the previous year, polypharmacy prevalence was 26,2%, 78.1% patients lived alone or with partner and 24.5% were not satisfied with his/her life. Mean albumin measurement was 4.3 (0.4) g/L. The FUNCFRAIL score model included the following variables: age 65 or over [2 points]; polypharmacy (5 or more medications excluding antiretrovirals) [2 points]; diabetes [1 point]; albumin < 4 g/L [2 points]; falls [1 point]; not being satisfied with his/her life [1 point]; and not living alone or with a partner [2 points]. The FUNCFRAIL score ranged

from 0 to 11 points, with higher values indicating a greater likelihood of being frail (Figure 1). The area under the ROC curve (AUROC 95% to discriminate frail patients was 0,78 (0,71-0,85).

**Conclusion:** The FUNCFRAIL Score is a simple tool to be used in daily clinical practice for frailty screening in older adults with HIV.

Figure 1. The FUNCFRAIL Score




Poster Abstracts

## 619 ASSOCIATION OF SLEEP DISRUPTION WITH KYNURENINE PATHWAY ACTIVATION IN WOMEN WITH HIV

New Investigator Scholar

**Andrea C. Rogando**[1], Kathleen Weber[2], Jiaqian Xing[3], Xiaonan Xue[3], Tsion Yohannes[4], Ralph Morack[2], Qibin Qi[3], Clary Clish[5], Kevin Bullock[5], Deborah Gustafson[6], Kathryn Anastos[3], Anjali Sharma[3], Helen J. Burgess[7], Audrey L. French[8]
*[1]Charles R Drew University of Medicine and Science, Los Angeles, CA, USA, [2]Hektoen Institute of Medicine/CORE Center of Cook County Health, Chicago, IL, USA, [3]Albert Einstein College of Medicine, Bronx, NY, USA, [4]Chicago Women's Interagency HIV Study, Chicago, IL, USA, [5]Broad Institute of MIT and Harvard, Cambridge, MA, USA, [6]State University of New York Downstate Medical Center Downstate Medical Center, Brooklyn, NY, USA, [7]University of Michigan, Ann Arbor, MI, USA, [8]Cook County Health & Hospitals System, Chicago, IL, USA*

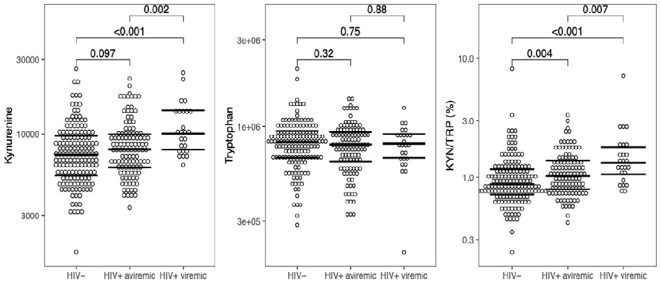
**Background:** Poor sleep is associated with HIV and women living with HIV (WLWH) are particularly affected, although mechanisms are unclear. We explored the association between sleep disruption and tryptophan-kynurenine (T/K) pathway activation, measured by the K:T ratio.

**Methods:** HIV-uninfected women (HIV-) and WLWH on stable ART aged 35-70 years were recruited from the Chicago, Bronx, and Brooklyn Women's Interagency HIV Study (WIHS) sites and clinical care settings. Women wore a wrist actigraph device for 10 days. Plasma T/K pathway metabolites were measured using liquid chromatography tandem mass spectrometry (Broad Institute, Harvard/MIT). Plasma sandwich ELISA was performed in duplicate to quantify concurrent sCCL2/MCP-1, TNF-α RII, hs-CRP, hs IL-6, sCD14 and sCD163. Multivariate linear regression was used to examine relationships between K:T and actigraph sleep metrics by HIV status controlling for age and race. Comparisons used chi-squared or Fisher's exact test for categorical variables and two-sample t-test or Wilcoxon rank-sum test for continuous variables.

**Results:** Among 153 WLWH and 151 HIV- women, mean age was 52.7 years, 75% were Black, 68% had annual household income <$18,000, and 40% had less than high school education. Demographics were similar between WLWH and HIV- women. For WLWH, median CD4 was 751 c/mL; 92% had HIV RNA<20 copies/mL. Compared to HIV-, WLWH had higher K:T and kynurenine with viremic WLWH having highest values (Figure); tryptophan levels did not differ between groups. Regression analysis showed that higher K:T was associated with more wake bouts (p<0.001), greater sleep fragmentation (p=0.001), and lower sleep efficiency (p=0.005) in WLWH only. In WLWH, K:T was associated with earlier sleep onset (p=0.01). In HIV- women, higher K:T was associated with longer total sleep time (p=0.047). In WLWH, K:T correlated with higher plasma TNF-α (p<0.001), IL-6 (p<0.001), CD163 (p<0.01), and CD14 (p<0.05).

**Conclusion:** In a study of well-matched WLWH and HIV- women, we found that HIV, particularly viremia, was associated with T/K pathway activation; this activation correlated with markers of inflammation/monocyte activation and was associated with poorer sleep efficiency and more fragmented sleep. While longitudinal studies are needed to elucidate the directionality of these associations, these findings may help identify treatments to reduce sleep disruption in HIV by targeting residual inflammation and T/K pathway activation.

FIGURE: Plasma tryptophan, kynurenine, and kynurenine:tryptophan ratio in 285 women: Pairwise comparison between HIV+ aviremic groups or HIV+ viremic group vs. HIV-uninfected group




## 620 SLEEP AND FRAILTY AMONG MEN WITH AND WITHOUT HIV

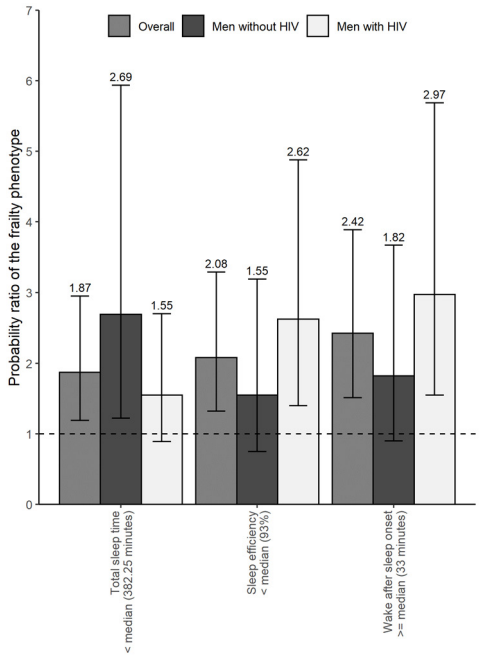
**Mary Clare C. Masters**[1], Benjamin Barrett[2], Gypsyamber D'Souza[2], Joshua Hyong-Jin Cho[3], Sanjay R. Patel[4], Valentina Stosor[1], Naresh M. Punjabi[5], Frank Palella[1]
*[1]Northwestern University, Chicago, IL, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]University of Pittsburgh, Pittsburgh, PA, USA, [5]University of Miami, Miami, FL, USA*

**Background:** Persons with HIV (PWH) experience earlier onset and increased rates of frailty compared to those without HIV. Poor sleep quality has been associated with frailty in the general population. However, data are needed assessing associations between objective measures of sleep quality and frailty among PWH.

**Methods:** The Multicenter AIDS Cohort Study (MACS) is a prospective study of men with or at risk for HIV. MACS participants underwent semi-annual Fried Frailty phenotype assessment, including measures of grip strength, gait speed, activity, exhaustion, and weight loss. Frailty is defined as ≥ 3 Fried criteria. In 2018, a subset of participants underwent actigraphy-based sleep assessments for total sleep time (TST), sleep efficiency (i.e., total sleep time/time in bed), and wake after sleep onset (WASO, i.e., time awake after sleep onset). These measures were dichotomized using median cut-point. The analysis examined cross-sectional associations between sleep quality and nearest measure of frailty using Poisson regression models with robust variance estimates and adjusted for age, BMI, and type 2 diabetes. Models including men living with HIV (MLWH) and without HIV (MWOH) were also adjusted for HIV serostatus.

**Results:** Of 802 men, 56% were living with HIV. Median age was 56 and 63 years, respectively, in those with HIV and without. More MLWH were frail (11%) than MWOH (8%). In MLWH, 96% had suppressed plasma HIV-1 RNA (<500 copies/mL). Among all participants, probability of frailty was significantly increased among those with low TST (adjusted probability ratio [aPR]=1.87 [95% CI: 1.19, 2.95]); low sleep efficiency (aPR=2.08 [95% CI: 1.32, 3.29]); and high WASO (aPR=2.42 [95% CI: 1.51, 3.89]), all p<0.01. Among MLWH, similar associations were seen between frailty and low sleep efficiency (aPR=2.62 [95% CI: 1.40, 4.88]) and high WASO (aPR=2.97 [95% CI: 1.55, 5.69]), all p<0.01. Among MWOH, low TST was significantly associated with frailty (aPR=2.69 [95% CI: 1.22, 5.94], p=0.01) (Figure).

**Conclusion:** Objective measures of poor sleep were associated with increased frailty risk in both men with and without HIV. Greater probability of frailty was significantly associated with reduced sleep efficiency and elevated nighttime wakening in MLWH and lower TST in MWOH. These data suggest that interventions to improve sleep health may be an avenue to prevent development of or treat frailty among MLWH.




## 621 POOR SLEEP IS LINKED TO CVD RISK IN PLWH IN A SOUTHWESTERN US CLINIC

New Investigator Scholar

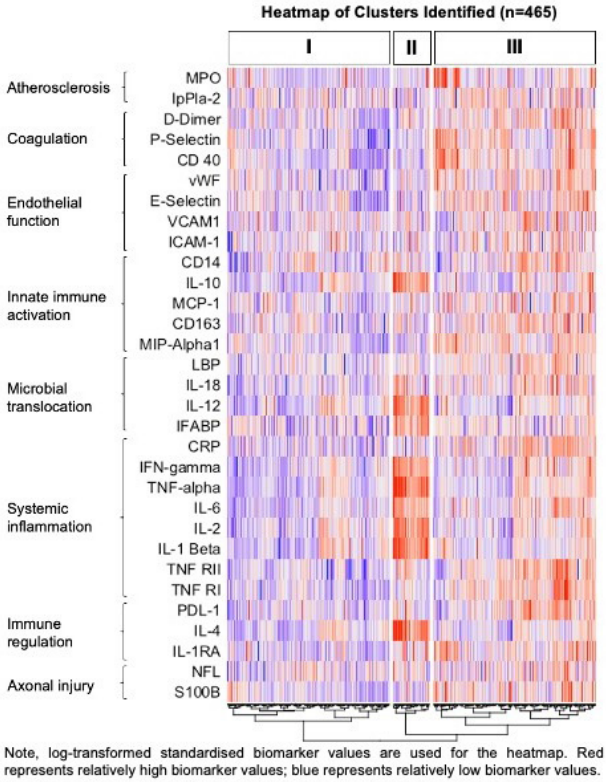
**Rita A. Bedrossian**[1], Julia Fisher[1], Ryan Weltzer[1], Rachel Briggs[1], Anna C. Ressel[1], Marine Khachatryan[1], Jacob C. Matthews[1], Bao Q. Thai[1], Jagteshwar Tung[2], Michael Grandner[1], Freda Patterson[3], Elizabeth Connick[1]
*[1]University of Arizona, Tucson, AZ, USA, [2]St George's University, True Blue, Grenada, [3]University of Delaware, Newark, DE, USA*

**Background:** Poor sleep health is a non-traditional risk factor for cardiovascular disease (CVD) in the general population. People living with HIV (PLWH) have poorer sleep health and elevated CVD risk as compared to non-PLWH, but the extent to which poor sleep health relates to CVD risk is unknown. To address this, we investigated correlates of poor sleep health including CVD risk in outpatients at an HIV clinic in Tucson, AZ.
**Methods:** PLWH (n=150) completed an electronic survey assessing sleep health [sleep duration, sleep latency (time to fall asleep), wake after sleep onset (WASO), naps, difficulty with falling asleep/staying asleep/waking up too early, satisfaction with current sleep pattern, desire to improve sleep], demographics, family history, and tobacco use. Clinical data were abstracted from the EHR including CD4 count, HIV RNA, diabetes history, BMI, blood pressure (BP), and lipids. 5- and 10-year CVD risk scores were calculated using the reduced Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D-R) model. Data were analyzed using Fisher exact tests and regression models.
**Results:** Participants were: 88% male at birth; 53% White non-Latinx; 27% Latinx, 14% Black, 2% Asian, 5% multi-racial; median age 52 years (range, 20-82); median CD4 count 638 cells/$mm_3$; 92% HIV RNA<50 copies/mL; 25% current tobacco users; median BMI 27.8. Median sleep duration was 6.5 h/night (IQR 5-7.25); 27% had sleep latency ≥30 min; 27% had WASO ≥30 min; 34% took naps; 44% had difficulty falling asleep; 41% had difficulty staying asleep; 31% had problems waking early; 67% were unsatisfied with their current sleep; and 81% were interested in improving sleep. Age, viral load, LDL, triglycerides, BMI, and smoking were not associated with sleep health metrics. Higher CD4 count was associated with difficulty falling asleep (p=0.007), waking early (p=0.028), sleep dissatisfaction (p=0.016) and desire to improve sleep (p=0.005). Higher systolic BP was associated with shorter sleep (p=0.053); higher diastolic BP was associated with shorter sleep (p=0.046), increased sleep latency (p=0.010), increased WASO (p=0.036), and difficulty falling asleep (p=0.048); diabetes was associated with shorter sleep (p=0.020). Higher 5- and 10-year CVD risk scores were associated with shorter sleep (p=0.024 and p=0.027, respectively).
**Conclusion:** Sleep disturbances were pervasive in PLWH. Greater CVD risk was associated with shorter sleep, which likely augments CVD risk. Interventions to improve sleep health could reduce CVD in PLWH.

## 622 EXTERNAL VALIDATION OF BIOMARKER CLUSTERS BASED ON PROTEIN BIOMARKERS

**Nicholas Bakewell**[1], Caroline Sabin[1], Nicki D. Doyle[2], Alejandro A. Garcia[3], Riya Negi[3], Frank A. Post[4], Jane Anderson[5], Jaime Vera[6], Marta Boffito[7], Lewis Haddow[8], Memory Sachikonye[9], Alan Winston[2], Patrick Mallon[3], Ken Kunisaki[10]
*[1]University College London, London, UK, [2]Imperial College London, London, UK, [3]University College Dublin, Dublin, Ireland, [4]King's College London, London, UK, [5]Homerton University Hospital NHS Trust, London, UK, [6]Brighton and Sussex Medical School, Brighton, UK, [7]Chelsea and Westminster NHS Foundation Trust, London, UK, [8]Kingston Hospital NHS Foundation Trust, Surrey, UK, [9]UK Community Advisory Board (UK-CAB), London, UK, [10]University of Minnesota, Minneapolis, MN, USA*

**Background:** People with HIV (PWH) exhibit chronic inflammation which may contribute to comorbidities. Using data from the POPPY study, we validate biomarker patterns identified in a previous independent smaller cohort of PWH and HIV-negative controls (McGettrick, CROI 2021).
**Methods:** The POPPY cohort includes 3 groups (PWH≥50 yrs, PWH<50 yrs and HIV-ve controls ≥50 yrs) in England/Ireland. We measured 31 biomarkers, covering inflammatory pathways of systemic inflammation, axonal injury, immune regulation, microbial translocation, innate immune activation, endothelial function, coagulation and atherosclerosis. Following Principal Component Analysis of the log-transformed biomarkers, agglomerative clustering was used to group participants based on component scores. Between-cluster demographic and clinical differences were assessed for significance using Kruskal-Wallis/Chi-squared tests.
**Results:** The 465 included participants (236 PWH≥50, 107 PWH<50, 122 HIV-ve) had a median (interquartile range [IQR]) age 54 [50-60] years, 80% were male, 88% white, 71% men having sex with men (MSM) and median [IQR] CD4 cell count (for PWH) was 610 [470-785] cells/$mm_3$. Three clusters displaying distinct patterns of inflammatory biomarkers were identified: Cluster 1 (n=209, 45% of subjects) included those with generally low levels of inflammation; Cluster 2 (n=47, 10%) included those with increased markers associated with T-cell and B-cell activation and proliferation, and Cluster 3 (n=209, 45%) identified those with elevated levels of biomarkers across a range of inflammatory pathways (Figure). Those in each cluster were similar for most demographic/lifestyle variables: median age (54, 56 and 55 yrs, p=0.08); male (82%, 68%, 81%, p=0.08); white (90%, 87%, 85%, p=0.26); MSM (74%, 64%, 70%, p=0.33); and current alcohol use (84%, 87%, 80%, p=0.45). However, there were significant differences for HIV status (73%, 60%, 78%, p=0.03); obesity (BMI≥30 kg/$m_2$) (11%, 21%, 24%, p=0.002); median systolic blood pressure (126, 135, 126 mmHg, p=0.002); and history of cardiovascular disease (39%, 28%, 53%, p=0.001) and arthritis of knee/hip (8%, 9%, 16%, p=0.02).
**Conclusion:** The 3 clusters of distinct inflammatory patterns, associated with differences in important cardiometabolic features suggests the presence of biological phenotypes that may contribute to clinical outcomes. Whether this personalised approach can inform disease prevention and improved treatment for PWH with multimorbidity requires further study.




Note, log-transformed standardised biomarker values are used for the heatmap. Red represents relatively high biomarker values; blue represents relatively low biomarker values.

## 623 NETWORK ANALYSIS HIGHLIGHTS DIFFERENTIAL CLINICAL AND OMICS PROFILES IN HIV INFECTION

New Investigator Scholar

**Flora Mikaeloff**[1], Marco Gelpi[2], Andreas D. Knudsen[2], Beate Vestad[3], Julie Høgh[2], Johannes R. Hov[4], Thomas Benfield[5], Daniel Murray[6], Marius Trøseid[7], Susanne D. Nielsen[2], Ujjwal Neogi[1]

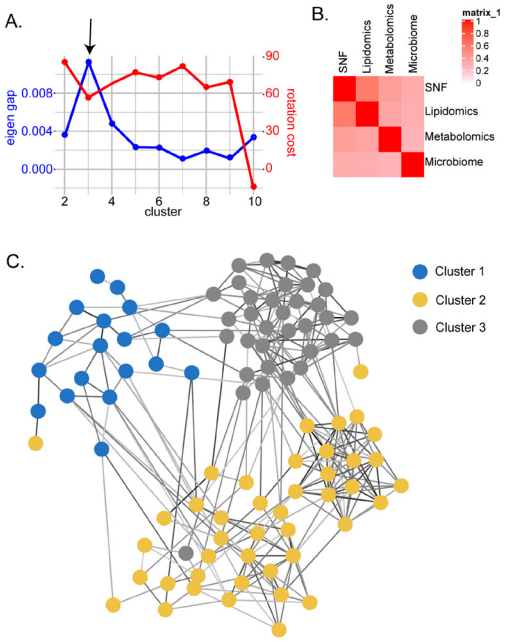
*[1]Karolinska Institute, Stockholm, Sweden, [2]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, [3]Oslo University Hospital, Oslo, Norway, [4]Oslo University Hospital Rikshospitalet, Oslo, Norway, [5]Danish Medical Journal, Copenhagen, Denmark, [6]Centre for Health and Infectious Diseases Research, Copenhagen, Denmark, [7]Institute of Clinical Medicine, Oslo, Norway*

**Background:** Some people living with HIV under long-term successful antiretroviral therapy (PLWH) suffer from cardiometabolic comorbidities, among other aging-related disorders. Though case-control studies comparing PLWH and HIV-negative control (HC) have been done previously, the heterogeneity among PLWH related to the incidence of metabolic diseases has not been investigated. To predict metabolic changes in PLWH, we aim to determine clusters of patients based on three omics layers integration and the underlying mechanisms separating these clusters using advanced network analysis.

**Methods:** Samples from 97 patients from the Copenhagen Comorbidity in HIV-infection (COCOMO) study and 20 age, BMI, and gender-matched HC were used for this study. The clinical data were collected from the COCOMO database, untargeted plasma metabolomics and lipidomics were performed using ultra-high-performance liquid chromatography/mass spectrometry (UHPLC/MS/MS) and microbiome profiling by bacterial 16S rRNA analyses. PLWH were clustered based on three layers integration (metabolome, lipidome and microbiome) using similarity network fusion (SNF). The clusters were then characterized by clinical parameters and the individual omics levels using advanced statistics.

**Results:** Three clusters (C1-C3) of PLWH were identified based on SNF (Fig 1A-C). Lipids were shown to have the most influence in the cluster repartition (Fig 1B). C1 and C3 include patients with the healthiest profile compared to C2. C2 represented patients with high BMI, metabolic syndrome, high visceral adipose tissue, subcutaneous adipose tissue (SAT) and hypertension (all $p<0.05$) but interestingly also had a higher CD4 count ($p<0.05$). C3 showed similar metabolomics and lipidomics profiles like HC. At clinical level, patients from C3 have higher BMI and SAT than C1 but lower than C2. C2 showed a drastic increase in triglycerides and diglycerides compared to C1 and C3 (FDR<0.1). At microbiome level, alpha diversity of HC, C2 and C3 were almost similar while C1 was significantly lower. C2 was also enriched in Prevotella genus compared to C1 and C3 and have patients with men who have sex with men.

**Conclusion:** In conclusion, we have shown that the molecular heterogeneity among the patients should be considered while defining immunological and virological success to determine the healthy state as PLWH displayed different profiles at -omics and clinical levels. Certain patients have dysregulated metabolic profiles despite having suppressed viral load and high CD4.




## 624 EFFECT OF TENOFOVIR ON T-CELL MATURATIONAL SUBSETS IN LONG-TERM AVIREMIC HIV ADULTS

New Investigator Scholar

**Javier Rodriguez-Centeno**[1], Andrés Esteban-Cantos[1], Julen Cadiñanos[1], Rocio Montejano[1], Natalia Stella-Ascariz[1], Rosa De Miguel[1], Beatriz Mena-Garay[1], Gabriel Saiz-Medrano[1], Belen Alejos[2], Maria Jimenez-Gonzalez[1], Jose I. Bernardino[1], Juan M. Castro-Álvarez[1], Berta Rodes[1], Jose R. Arribas[1]

*[1]Hospital La Paz Institute for Health Research, Madrid, Spain, [2]Institute of Health Carlos III, Madrid, Spain*

**Background:** We have reported that HIV adults receiving antiretroviral therapy who maintain virological suppression for 10 years experience blood telomere length gains (JID 2017;76:102). However, telomere length increases were lower in participants treated with tenofovir (TFV) than in those treated with TFV-sparing regimens. It remains unknown if this difference is due to an interference with the immune reconstitution process that shifts T-lymphocyte subpopulations towards less mature T-cell lymphocytes with longer TL.

**Methods:** Longitudinal cohort of long-term aviremic HIV adults. For this analysis we selected participants continuously receiving TFV during the last 6 years or never exposed to TFV. We tested by flow cytometry at year 4 and at year 6 of follow-up CD4 and CD8 T-cell subsets from fresh PBMCs: Recent Thymic Emigrants (RTE) CD4+ cells (CD31+CD45RA+CD27+), naïve (CD45RA+CD27+), central memory (CD45RA-CD27+), effector memory (CD45RA-CD27-), TEMRA (CD45RA+CD27-), senescent (CD28-CD57+) and exhausted (PD1+).

**Results:** 108 participants were included (TDF n=15, TAF n=26, Abacavir n=49, N(t)RTI-sparing regimens n=18): 77.1% male and 92.7% Caucasian. At year 4 of follow-up: age (y) 52.8 (IQR 49.1 57.1), years since HIV diagnosis: 21.1 (IQR 16.4 25.5), time with virological suppression (y) 11.4 (IQR 10.7 11.8) and CD4 and CD8 T (cells/µL): 774 (IQR 585 970) and 630 (IQR 448 823). Nadir (cells/µL): 183 (IQR 105 273). Adjusting for sex, race, nadir, CMV serology, time of follow up and additionally by age, years since HIV diagnosis and percentage of the appropriate T-cell subset at baseline, participants treated with TFV had significantly lower decrease of exhausted CD4 T-cells (%) between year 4 and 6 of follow-up: -6.8 (IQR -13.4 -2.1) than participants not receiving TFV: -7.9 (IQR -13.3 -3, $P = 0.04$). Moreover, the percentage of exhausted CD8 T-cells increased in participants treated with TFV: 0.9 (IQR -5.2 5.0) and decreased in participants never exposed to TFV: -3.4 (IQR -8.8 4.6, $P < 0.001$). No differences were observed in the other T-cell maturational subsets between groups.

**Conclusion:** In long-term aviremic HIV adults, TFV treatment was associated with a lower longitudinal decrease in the percentage of exhaustion in CD4 T-cells and an increase in the percentage of exhausted CD8 T-cells. Further studies are needed to elucidate the relevance and the mechanisms underlying this biological phenomenon.

## 625 TENOFOVIR ALAFENAMIDE IS ASSOCIATED WITH SHORTER TELOMERE LENGTH IN PEOPLE WITH HIV

**Upal Roy**[1], Avery Matthews[2], Asante R. Kamkwalala[3], Ankita Garg[4], Hansapani Rodrigo[1], David Clifford[5], Benjamin B. Gelman[6], Christina M. Marra[7], Susan Morgello[8], Leah H. Rubin[3], Donald Franklin[9], Robert K. Heaton[9], Jue Lin[10], Ronald J. Ellis[9], Scott L. Letendre[9]

*[1]University of Texas Rio Grande Valley, Brownsville, TX, USA, [2]University of Texas at San Antonio, San Antonio, TX, USA, [3]The Johns Hopkins University, Baltimore, MD, USA, [4]University of Georgia, Athens, GA, USA, [5]Washington University in St Louis, St Louis, MO, USA, [6]University of Texas at Galveston, Galveston, TX, USA, [7]University of Washington, Seattle, WA, USA, [8]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [9]University of California San Diego, San Diego, CA, USA, [10]University of California San Francisco, San Francisco, CA, USA*

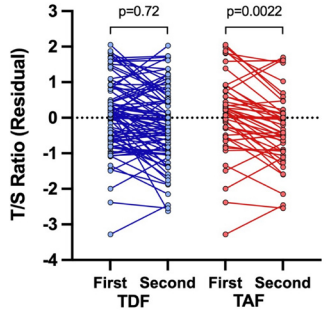
**Background:** People with HIV (PWH) are at high risk of aging-related diseases even while receiving antiretroviral therapy (ART). This premature aging might be reflected by biological aging biomarkers, one of which is telomere length, which is maintained by telomerase, a reverse transcriptase (RT) that can be inhibited in vitro by RT inhibitors, such as tenofovir (TFV). We investigated the impact of TFV on telomere length change in PWH over more than a decade.

**Methods:** 121 PWH were taking ART and were assessed between 2003 and 2007 with comprehensive assessments and then re-assessed after a median 12.4 years in the CHARTER project. The most commonly used ART drugs at the second visit were emtricitabine (FTC, 65.3%), TFV alafenamide (TAF, 38.8%), dolutegravir (35.5%), lamivudine (25.6%), abacavir (24.8%), and darunavir (20.7%). Telomere length was measured in blood-derived cells by qPCR and was analyzed as the telomere to beta-globin single copy gene (T/S) ratio by mixed effects models that adjusted for demographic and disease characteristics as well as leukocyte count and duration of follow-up.

**Results:** At the second visit, median age was 56 years, 11.7% were women, 43.3% were black, 94.0% had HIV RNA in plasma ≤ 200 cp/mL, and median CD4+ T-cells were 583/µL (current) and 64/µL (nadir). Median T/S ratio was 0.96 (IQR 0.84, 1.08) at the first visit and declined at the second visit (median -0.082, IQR (-0.02)-(-0.19), p<10-16). The T/S ratio of PWH who used TFV, either disoproxil fumarate (TDF, n=111 of 242 visits [45.9%]) or TAF (n=47 at the second visit only), declined more over time than of those who did not use tenofovir (p=0.049). Additional analysis identified that TAF (p=0.0022) but not TDF (p=0.72) was associated with greater T/S ratio decline (see Figure), even after multivariable adjustment (p=0.035). The only other ART drug that was associated with T/S ratio change was FTC (p=0.038) but the p value weakened (p=0.44) after adjusting for TAF use. Adjusting for use of FTC or other ART drugs did not weaken the relationship between TAF and T/S ratio.

**Conclusion:** PWH who use TAF have greater decline in telomere length than PWH who do not use TAF, even after accounting for demographic and disease characteristics. The inconsistent findings between TAF and TDF may be because intracellular TFV concentrations are higher with TAF than with TDF. A limitation is that TAF was not used at the first visit since it was not yet approved for clinical use so the findings should be confirmed in controlled trials.

**Figure:** T/S ratio at the first and second visits for participants who either used TDF or TAF. Values are the residuals after adjustment of T/S ratio for age, sex, race/ethnicity, and leukocyte count.




## 626 POST-ACUTE SEQUELAE OF SARS-CoV-2 IN NONHOSPITALIZED ACTIV-2 TRIAL PARTICIPANTS

**Teresa H. Evering**[1], Busola Sanusi[2], Nikolaus Jilg[3], Eunice Yeh[2], Carlee B. Moser[2], David A. Wohl[4], Eric S. Daar[5], Paul Klekotka[6], Arzhang Cyrus Javan[7], Joseph J. Eron[4], Judith S. Currier[8], Michael Hughes[2], Davey M. Smith[9], Kara W. Chew[8]

*[1]Weill Cornell Medicine, New York, NY, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [5]Lundquist Institute at Harbor-University of California Los Angeles Medical Center, Torrance, CA, USA, [6]Eli Lilly and Company, San Diego, CA, USA, [7]National Institutes of Health, Bethesda, MD, USA, [8]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA, [9]University of California San Diego, San Diego, CA, USA*

**Background:** Randomized COVID-19 trials provide opportunities to describe post-acute sequelae of SARS-CoV-2 (PASC)-related symptom burden longitudinally and assess the impact of early use of antivirals on PASC prevalence.

**Methods:** ACTIV-2 evaluates safety and efficacy of investigational agents for non-hospitalized adults with mild to moderate COVID-19 in a Phase II/III trial. In Phase II, participants were randomized within 10 days of symptom onset and a positive SARS-CoV-2 virologic test to receive bamlanivimab (BAM) or placebo as a single infusion at 7000mg (n=94) or 700mg (n=225). In a subsequent single-arm open-label study, 1059 participants received 700mg BAM. Participants completed a 13-symptom daily diary from enrollment through Day 28. A long-term (LT) diary (14 additional symptoms) introduced after the study was underway was completed by a subset of individuals every 12 weeks. We report Week 24 findings.

**Results:** Between Aug 2020 to Feb 2021 605 participants enrolled and completed LT diary at Week 24 [Phase II: 7000mg vs. placebo (n=25); 700mg vs. placebo (n=68); single-arm open-label cohort: 700mg (n=512)]. Median age was 50 years, 51% female sex, 99% identified as cis-gender, 5% Black/African American, and 35% Hispanic/Latino. At enrollment, 53% reported ≥1 high-risk comorbidity and 0.3% were vaccinated against COVID-19. By Week 24, 14% (87/605) had not returned to their pre-COVID-19 health by self-report, with 57% (50/87) reporting ≥3 PASC symptoms. The most common symptoms were fatigue (45% of 87), smell disorder (36%), breathing difficulties (30%), taste disorders (25%), musculoskeletal pain (26%) or weakness (23%), and cognitive complaints: difficulty concentrating/thinking (30%), difficulty reasoning and solving problems (21%), memory loss (25%) and insomnia (23%). Most reported symptoms as "mild". Participants who reported acute viral illness symptoms between Days 22-28 were more likely to report PASC symptoms at Week 24 than those who did not report symptoms at Days 22-28 [51% (164/320) vs. 27% (76/285); p<0.0001].

**Conclusion:** In outpatients with mild to moderate COVID-19, 14% had not returned to pre-COVID-19 health by 24 weeks post infection, with generally mild but multiple symptoms. Presence of acute viral illness symptoms at 3-4 weeks was associated with an increased risk of PASC symptoms months later. Larger placebo-controlled studies within ACTIV-2 will assess the potential for early antiviral therapies to mitigate or prevent PASC.

## 627 CLINICAL CONDITIONS ASSOCIATED WITH PASC IN KAISER PERMANENTE MID-ATLANTIC STATES

**Eric S. Watson**[1], Michael A. Horberg[1], Celeena R. Jefferson[1], Julia M. Certa[1], Keri N. Althoff[2], Carolyn F. Williams[3], Richard Moore[2]

*[1]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA*

**Background:** The natural history of the longer-term effects of SARS-CoV-2 (COVID-19), known as Post-Acute Sequelae of SARS-CoV-2 (PASC), is limited. Disease characterization and definition changed over time and identification via standard diagnosis codes was only recently enacted. We aim to identify a cohort of individuals with, or at-risk for, PASC among Kaiser Permanente Mid-Atlantic States (KPMAS) members, and to identify the clinical conditions of greater burden for those with PASC.

**Methods:** Within our electronic health record system (including internal/external records), we identified adult patients (≥18 years) who had a detectable SARS-CoV-2 RT-PCR result between 1/1/2020–12/31/2020. Non-COVID disease diagnoses/conditions were categorized into specific time intervals based on the first positive SARS-CoV-2 test as the index date (T0), defined as: 1) "prevalent":

diagnoses in 4 years prior to T0 and excluded from later consideration; 2) "persistent/acute": new disease diagnoses 0-30 days post-T0 and persisted 30-120 days further, and not included as prevalent; 3) "incident/late": new disease diagnoses 30-120 days post-T0, not previously identified as prevalent or persistent/acute. Diagnoses were grouped using Clinical Classification Software (CCS) to isolate conditions for PASC. Final CCS distributions were computed relative to the condition counts for each time interval, validated by infectious disease physicians to identify conditions of focus (COF).

**Results:** From the resulting 31,390 patients, we identified the 14 most common COF (Table 1). The most common persistent/acute COF were other lower respiratory disease (4.5%) and respiratory failure (2.7%). Most common incident/late COF (i.e., >2.0% of those testing COVID+) were abdominal pain, gastrointestinal disorders, other nervous system disorders, nonspecific chest pain, dizziness or vertigo, malaise and fatigue, anxiety disorders, mental health disorders, other lower respiratory disease (not previously diagnosed), and cardiac dysrhythmias. No other COF were >2.0% in the persistent or incident time periods.

**Conclusion:** We have identified conditions clinically associated with COVID-19 that persist from infection or present as incident beyond the acute COVID-19 period. This condition list should be utilized in clinical practice when following up with COVID-19 patients. Further research is needed to understand how these conditions compare to people who did not have COVID-19 and to describe their severity, persistence, and resolution.

**Table 1. Clinical Classification Software (CCS) Distributions by Time Period**

| CCS Category | Incident | Persistent | Prevalent |
|---|---|---|---|
| Abdominal pain | 4.40% | 0.70% | 2.90% |
| Gastrointestinal Disease | 4.30% | 1.60% | 2.90% |
| Other nervous system disorders | 4.30% | 0.90% | 2.70% |
| Nonspecific chest pain | 4.30% | 1.40% | 1.60% |
| Conditions associated with dizziness or vertigo | 4.20% | 0.90% | 3.10% |
| Malaise and fatigue | 3.50% | 1.00% | 0.80% |
| Other lower respiratory disease | 2.80% | 4.50% | 10.40% |
| Anxiety disorders | 2.80% | 0.90% | 2.30% |
| Mental health | 2.70% | 0.60% | 3.20% |
| Cardiac dysrhythmias | 2.30% | 1.20% | 1.30% |
| Nausea and vomiting | 1.70% | 0.30% | 0.50% |
| Other nutritional; endocrine; and metabolic disorders | 1.20% | 0.20% | 0.30% |
| Fluid and electrolyte disorders | 1.00% | 0.90% | 0.50% |
| Anosmia | 0.73% | 0.05% | 0.01% |
| Respiratory failure; insufficiency; arrest (adult) | 0.20% | 2.70% | 0.20% |

Time periods were defined as follows: Incident: 30-120 days post COVID+ test date; Persistent 0-30 days post COVID+ test date and persisted 30-120 days; Prevalent: 4 years prior to COVID+ test date

## 628 PERSISTENT COVID-19 SYMPTOMS ARE HIGHLY PREVALENT 12 MONTHS AFTER HOSPITALIZATION

**Catherine Chirouze**[1], Delphine Bachelet[2], Jean sebastien Hulot[3], Minerva Cervantes-Gonzalez[2], Francois Goehringer[4], Adrien Lemaignen[5], Mylene Maillet[6], Pierre Delobel[7], Matthieu Revest[8], Xavier Duval[2], Cedric Laouenan[2], Jade Ghosn[2]
*[1]Centre Hospitalier Régional Universitaire Jean Minjoz, Besabçon, France, [2]Bichat University Hospital, Paris, France, [3]Hôpital Européen Georges-Pompidou, Paris, France, [4]Centre Hospitalier Régional Universitaire Nancy, Nancy, France, [5]Centre Hospitalier Régional Universitaire Tours, Tours, France, [6]Centre Hospitalier Annecy, Annecy, France, [7]Centre Hospitalier Universitaire Toulouse, Toulouse, France, [8]Centre Hospitalier Universitaire Rennes, Rennes, France*

**Background:** Persistent COVID-19 symptoms have been reported up to six months (M6) after hospital discharge. Little is known on the frequency and the nature of persistent symptoms beyond M6. Here we assessed, in the longitudinal prospective French COVID-19 cohort, symptoms that persisted twelve months after admission for COVID-19.

**Methods:** Hospitalized patients with a virologically-confirmed COVID-19 were enrolled. Follow-up was planned with a physician's visit at M3, M6 and M12 post-admission. At M12, manual assessment of muscle strength of each limb was assessed using the modified Medical Muscle Research council Scale for testing muscle strength (mMRC). Patients were also interviewed on health-related quality-of-life (SF-12) and on psychological distress (HADS). Associations between persistence of ≥ 3 symptoms at M12 and clinical characteristics at admission were assessed through bivariate and multivariate logistic regression.

**Results:** By September 2021, M12 data were available for 737 patients enrolled between February 3rd and July 15th 2020. Median age was 61 years, 64% were men and 37% were admitted to intensive care unit during the acute phase. At M12 visit, 27% of participants had ≥ 3 symptoms, with no change between M6 and M12 globally. Fatigue (46%), dyspnea (33%) and joint pain (21%) were the 3 most frequently reported symptoms. Presence of ≥ 3 symptoms was associated with both anxiety and depression, an impaired quality of life and mMRC scale < 57. The mean percentage of predicted value of distance walked in 6 min (6MWT) was 88% (IQR 74 – 100) for the 163 patients who realised the 6MWT, this percentage was lower in patients who reported dyspnea (85% [IQR 71; 99] vs 95% [IQR 76; 101], p=0.04). Compared to men, women more often reported presence of ≥ 3 symptoms (39% vs 21%), depression and anxiety (respectively, 12% vs 6% and 21% vs 10%), an altered quality of life for the physical component only (54% vs 46%), and a slight or a moderate disability (respectively, 20% vs 14% and 6% vs 4%). Women had less often returned to work than men (34% vs 23%).

**Conclusion:** A fourth of individuals admitted to hospital for COVID-19 still had ≥3 persistent symptoms at M12 post-discharge, with no improvement between M6 and M12. Also, 25% of those who initially had a professional occupation were not back to work at M12. Women reported more often ≥3 symptoms, suffered more from anxiety and depression, and had less often returned to work than men.

## 629 CHEST CT BODY COMPOSITION CHANGES AT 3 AND 6 MONTHS AFTER SEVERE COVID-19 PNEUMONIA

**Giulia Besutti**[1], Jovana Milic[2], Giovanni Dolci[2], Marta Ottone[1], Marco Massari[1], Guido Ligabue[2], Filippo Monelli[2], Massimo Pellegrini[2], Efrem Bonelli[1], Paolo Giorgi Rossi[1], Giovanni Guaraldi[2]
*[1]Azienda Unità Sanitaria Locale IRCCS di Reggio Emilia, Reggio Emilia, Italy, [2]University of Modena and Reggio Emilia, Modena, Italy*

**Background:** Muscle and fat mass loss as a consequence of protein catabolism and prolonged immobilization is frequent in critically ill patients. Post-COVID acute sarcopenia may be due also to inflammaging for the strong inflammatory reaction. The study aims were to describe changes in chest CT body composition parameters from baseline to follow-up CT scan in severe COVID-19 survivors, and to evaluate the impact of COVID-19 inflammatory burden on these changes.

**Methods:** Baseline (t0), 2-3 months (t1) and 6-7 months (t2) follow-up CT scan of severe COVID-19 pneumonia survivors were retrospectively reviewed to measure pectoralis muscle area (PMA) and density (PMD), liver-to-spleen ratio (LSR), and total, visceral, and intermuscular adipose tissue areas (TAT, VAT and IMAT) at T7-T8 vertebrae. C-reactive protein (CRP) curve integral was used to describe COVID-19 inflammatory burden, and its impact on body composition changes was evaluated in multivariable linear regression models adjusted for age, sex, and baseline TAT (index of general adiposity).

**Results:** At follow-up a decrease in mean PMA and in all mean body fat areas was registered, faster from t0 to t1, and slower from t1 to t2, with the exception of PMD, which increased (i.e. intramuscular fat decreased) only from t1 to t2 (Table). Mean VAT decrease was more conspicuous than mean TAT decrease. In models adjusted for age, sex, and baseline TAT, increasing CRP integral was significantly associated with higher PMA reduction (p=0,017 for delta t2-t0) and lower PMD increase (p=0.01 for delta t2-t0), higher LSR increase (i.e. higher steatosis decrease) (p<0.0001 for delta t1-t0, n.s. for delta t2-t0), and higher VAT decrease (p=0.035 for delta t2-t0), but not with TAT decrease. These associations were stronger in patients with higher VAT and lower LSR at baseline.

**Conclusion:** Muscle and fat loss after COVID-19 is faster in the first months, but slowly continues till 6-7 months. Fat loss is more apparent in visceral compartments. Inflammatory burden is associated with the degree of muscle and visceral/liver fat loss.

| | Mean (SD) | | | Mean (SD) | | |
|---|---|---|---|---|---|---|
| | T0 (Baseline) | T1 (2-3 months FU) | T2 (6-7 months FU) | Delta T1-T0 | Delta T1-T2 | Delta T2-T0 |
| Pectoral Muscle Area | 18.01 (6.69) | 17.23 (6.81) | 16.90 (6.48) | -0.78 (4.39) | -0.33 (3.70) | -1.11 (4.37) |
| Pectoral Muscle Density | 33.97 (9.94) | 33.82 (9.61) | 36.89 (9.76) | -0.15 (6.77) | 3.07 (7.14) | 2.92 (8.19) |
| Liver to Spleen Ratio | 0.98 (0.26) | 1.10 (0.24) | 1.14 (0.21) | 0.125 (0.220) | 0.042 (0.217) | 0.167 (0.242) |
| Total Adipose Tissue Area | 274.8 (133.2) | 273.1 (142.9) | 271.7 (148.2) | -1.67 (44.94) | -1.46 (41.33) | -3.13 (55.33) |
| Intermuscolar Adipose Tissue Area | 32.3 (16.7) | 31.6 (15.9) | 31.1 (16.7) | -0.75 (7.07) | -0.47 (7.11) | -1.21 (7.39) |
| Visceral Adipose Tissue Area | 41.4 (19.6) | 39.2 (18.5) | 37.8 (18.8) | -2.21 (8.25) | -1.34 (9.66) | -3.55 (10.07) |

## 630 POST-COVID19 QUALITY OF LIFE: LOW SATISFACTION WITH PHYSICAL AND MENTAL HEALTH STATUS

New Investigator Scholar

**Ilaria Mastrorosa**[1], Carmela Pinnetti[1], Giulia Del Duca[1], Patrizia Lorenzini[1], Alessandra Vergori[1], Marta Camici[1], Anna Clelia Brita[1], Valentina Mazzotta[1], Pierangelo Chinello[1], Paola Mencarini[1], Maria Letizia Giancola[1], Amina Abdeddaim[1], Enrico Girardi[1], Francesco Vaia[1], Andrea Antinori[1]

[1]*Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy*

**Background:** After the acute phase of infection, new, recurring or ongoing symptoms related to COVID19 may persist for weeks or months. Aims of our study were to size the impact of these symptoms on physical (PH) and mental (MH) health status and quality of life (QoL), reported by patients (pts), and to investigate factors influencing the perception of PH, MH, and QoL.

**Methods:** We included pts referred to the post-COVID19 outpatient service, with and without prior hospitalization (PHosp), evaluated at 3,6 and 12 months after the acute infection. Demographic, clinical and pharmacological data were collected in an electronic system. At each visit, the Short-Form 36-item questionnaire (SF-36), assessing the perception of PH and MH, and the Visual Analogue Scale (VAS), ranging from 0 to 100, of the EQ5D, assessing QoL, were administered. Student's T-test was employed for comparisons and linear regression was used to identify factors associated with PH, MH, and QoL. In a subgroup of patients, we assessed the presence of anxiety and depressive symptoms and sleep disturbances through the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI II) and the Pittsburgh Sleep Quality Index (PSQI) questionnaires, respectively.

**Results:** Out of a total of 914 assessments, we considered the first one of each pt (n=572): median (IQR) age of 55 years (47-62), 53% male, 38% with at least 1 comorbidity, 54% with PHosp, median distance from acute infection of 4.8 months (3.6-7.1). The mean of each subscale assessed in SF-36 was significantly lower than the normative values of the Italian population (Figure 1) and it remained stable over time. Female gender, the presence of comorbidities, and the use of corticosteroids during the acute infection were associated with a worse perception of PH, MH, and QoL; pts with PHosp reported a better MH overall (Figure 2). Alterations in BAI, BDI II, and PSQI were associated with worse perceptions of PH, MH, and HRQoL, in the subgroup of 265 patients in whom they were evaluated.

**Conclusion:** In our study, post-COVID19 pts reported a significantly worse perception of PH and MH status compared to the Italian normative group, and a higher risk was demonstrated for female pts, pts with comorbidities and pts treated with corticosteroids. Moreover, the presence of anxious-depressive symptoms and poor sleep quality was correlated to a worse perception of health status and QoL. A systematic monitoring of these aspects is mandatory to properly manage pts in the post-COVID19 period.

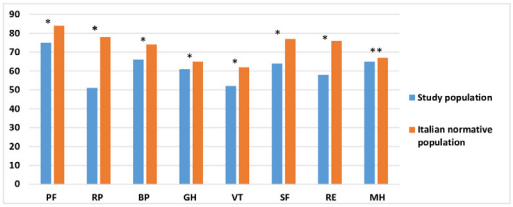



**Figure 2. Factors associated with higher scores in the physical (PH) and mental health (MH) *status*, as reported in the 36-Item Short Form Health Survey (SF-36), and with a better quality of life, as reported on a Visual Analogue Scale (VAS), ranging from 0 to 100 (0-100), by multivariable linear regression.** *Other variables analyzed: age, the use of Non-Invasive Ventilation, the use of remdesivir and heparin, number of months after the acute infection.*

| | PH | | | | MH | | | | VAS 0-100 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | beta | 95CI | | p-value | beta | 95CI | | p-value | beta | 95CI | | p-value |
| *Male vs female* | **16,64** | **12,71** | **20,57** | **0,000** | **15,53** | **11,73** | **19,33** | **0,000** | **10,28** | **7,12** | **13,45** | **0,000** |
| *Number of comorbidities* | | | | | | | | | | | | |
| *1* | **-7,99** | **-12,75** | **-3,24** | **0,001** | **-4,99** | **-9,59** | **-0,39** | **0,033** | **-4,79** | **-8,62** | **-0,95** | **0,015** |
| *2* | **-12,90** | **-21,03** | **-4,77** | **0,002** | **-9,91** | **-17,77** | **-2,05** | **0,014** | **-12,18** | **-18,74** | **-5,63** | **0,000** |
| *≥ 3* | **-27,63** | **-38,76** | **-16,50** | **0,000** | **-23,78** | **-34,54** | **-13,02** | **0,000** | **-17,13** | **-26,10** | **-8,16** | **0,000** |
| *Previous hospitalization* | 2,50 | -2,55 | 7,55 | 0,331 | **5,67** | **0,80** | **10,55** | **0,023** | 0,62 | -3,44 | 4,69 | 0,764 |
| *Therapy during the acute infection* | | | | | | | | | | | | |
| *corticosteroids* | **-10,18** | **-15,17** | **-5,18** | **0,000** | **-6,16** | **-10,99** | **-1,33** | **0,012** | **-5,55** | **-9,58** | **-1,53** | **0,007** |
| *remdesivir* | 3,89 | -1,96 | 9,74 | 0,192 | 3,67 | -1,99 | 9,32 | 0,203 | 3,14 | -1,57 | 7,85 | 0,191 |
| *Immunotherapy* | **-16,11** | **-31,60** | **-0,62** | **0,042** | -9,26 | -24,24 | 5,72 | 0,225 | -11,14 | -23,62 | 1,34 | 0,080 |
| *Heparin* | -1,24 | -6,82 | 4,33 | 0,661 | -4,80 | -10,19 | 0,59 | 0,081 | 2,76 | -1,74 | 7,25 | 0,228 |

## 631 NEUROLOGIC AND IMMUNOLOGIC BIOMARKERS ASSOCIATED WITH POST-COVID NEUROLOGIC SYMPTOMS

**Michael J. Peluso**[1], Hannah M. Sans[1], Carrie A. Forman[1], Ahmed Chenna[2], Brandon C. Yee[2], John W. Winslow[2], Christos Petropoulos[2], Jeffrey N. Martin[1], John D. Kelly[1], Meredith Greene[1], Felicia C. Chow[1], Joanna Hellmuth[1], Timothy J. Henrich[1], Dave Glidden[1], Steven G. Deeks[1]

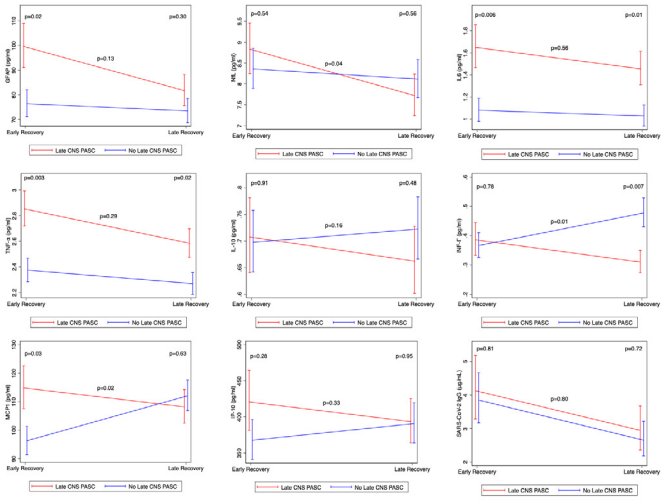
[1]*University of California San Francisco, San Francisco, CA, USA,* [2]*Monogram BioSciences, San Francisco, CA, USA*

**Background:** The biologic mechanisms underlying neurologic post-acute-sequelae of SARS-CoV-2 infection (PASC) are incompletely understood. We measured plasma markers of neuronal injury (glial fibrillary acidic protein [GFAP], neurofilament light chain [NfL]) and inflammation among a cohort of people with prior confirmed SARS-CoV-2 infection at early and late recovery following the initial illness (defined as < and > 90 days since COVID-19 onset, respectively). We hypothesized that those experiencing persistent neurologic symptoms would have elevations in these markers.

**Methods:** The primary clinical outcome was the presence of self-reported central nervous system (CNS) PASC symptoms during the late recovery timepoint. We compared fold-changes in marker values between those with and without CNS PASC symptoms using linear mixed effects models and examined relationships between neurologic and immunologic markers using rank linear correlations.

**Results:** Of 121 individuals, 52 reported CNS PASC symptoms. During early recovery, those who went on to report CNS PASC symptoms had elevations in GFAP (1.3-fold higher mean ratio, 95% CI 1.04-1.63, p=0.02), but not NfL (1.06-fold higher mean ratio, 95% CI 0.89-1.26, p=0.54). During late recovery, neither GFAP nor NfL levels were elevated among those with CNS PASC symptoms. Although absolute levels of NfL did not differ, those who reported CNS PASC symptoms demonstrated a stronger downward trend over time in comparison to those who did not report CNS PASC symptoms (p=0.041). Those who went on to report CNS PASC also exhibited elevations in IL-6 (48% higher during early recovery and 38% higher during late recovery), MCP-1 (19% higher during early recovery), and TNF-alpha (19% higher during early recovery and 13% higher during late recovery). GFAP and NfL correlated with levels of several immune markers during early recovery (MCP-1, IL-6, TNF-a, IFN-g); these correlations were attenuated during late recovery.

**Conclusion:** Self-reported neurologic symptoms present approximately four months following SARS-CoV-2 infection are associated with elevations in markers of neurologic injury and inflammation at early recovery timepoints, suggesting that early injury can result in long-term disease. The correlation of GFAP and NfL with markers of systemic immune activation suggests one possible mechanism that might contribute to these symptoms. Additional work will be needed to better characterize these processes and to identify interventions to prevent or treat this condition.



## 632 NEUROPSYCHOLOGIC PERFORMANCE FOLLOWING COVID-19: PREVALENCE AND PREDICTORS

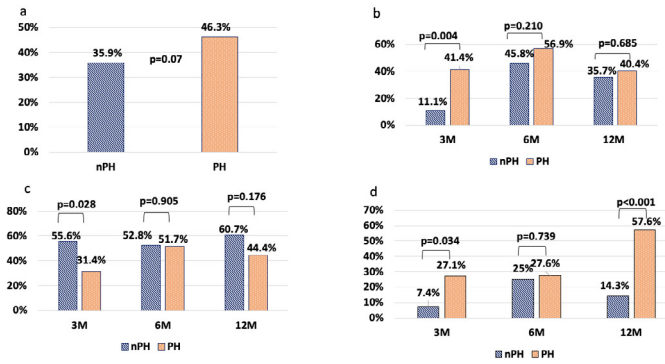
**Alessandra Vergori**[1], Carmela Pinnetti[1], Giulia Del Duca[1], Anna Clelia Brita[1], Ilaria Mastrorosa[1], Patrizia Lorenzini[1], Valentina Mazzotta[1], Marta Camici[1], Pierangelo Chinello[1], Paola Mencarini[1], Maria Letizia Giancola[1], Amina Abdeddaim[1], Enrico Girardi[1], Francesco Vaia[1], Andrea Antinori[1]

[1]*Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy*

**Background:** Insomnia, mood decline, anxiety, and cognitive impairment are described following COVID-19, and the mechanisms underlying these symptoms

are not fully clarified. Aims of this analysis were to describe prevalence and predictors of impaired neuropsychological performance after COVID-19.
**Methods:** We included patients referred to the post-COVID19 service with and without a previous hospitalization (PH and nPH, respectively) assessed at 3,6 and 12 months (3M,6M,12M) post-COVID19. Patients underwent to a comprehensive neuropsychological assessment using a standardized battery of 10 tests across 4 domains (speed of information processing, abstract/executive, attention/ working memory, memory). Neurocognitive impairment (NCI) was defined by: score >1 standard deviation (SD) below the mean on at least 2 tests, or >2 SD below 1 test. Change in NPZ-10 (mean, SD) was analyzed as an outcome. In addition, the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI) and the Pittsburgh Sleep Quality Index (PSQI) were administered. Mann-Whitney and Chi-square tests were used for comparisons, and logistic and linear regression were used to identify factors associated with test results.
**Results:** N=302 participants: median age of 55 years (IQR 47-61), 52% female, median education of 13 yrs (13-18), 63% with >1 comorbidity, 58% PH (mainly males, higher age and higher BMI vs nPH). Overall, the prevalence of NCI was 42%, higher in PH vs nPH (46% vs 36%; p=0.07) (Figure 1a) with a not statistically significant mean decrease of NPZ10 [-0.12 (0.49)]. More in detail, we observed a significant decrease of z-score in the speed of information processing domain in PH vs nPH [-0.29(0.48) vs -0.12(0.31); p<0.001]. NCI prevalence resulted significantly higher in PH vs nPH only at 3M (Figure 1b). A higher proportion of nPH vs PH complained anxiety (BAI>85%) at 3M [55.6% vs 31.4%); p=0.028], sleep disturbances were more frequent in PH vs nPH at 3 and 12M (Figure 1d,c). Male gender appear to be the only associated factor with a lower alteration of BAI>85% and PSQI>5 [OR 0.28 (0.12-0.65); p=0.003; 0.22 (0.09-0.52); p=0.001; respectively]. No predictors of NCI or BDI>85% were found.
**Conclusion:** Our preliminary data show a consistent prevalence of NCI, significantly higher in PH vs nPH. This finding remains quite stable up to 12 months of observation. Also a worse sleep quality in PH was observed. Women seem to be at higher risk of anxiety-depressive and sleep disorders than men.

**Figure 1. a) Proportions of NCI according to hospitalization status [not previously hospitalized (nPH) and previously hospitalized (PH)]; b) proportion of NCI, c) Beck Anxiety Inventory (BAI>85) and d) Pittsburgh Sleep Quality Index (PSQI>5) according to hospitalization status and timepoints evaluation [3 (3M), 6 (6M) and 12 months (12M) after COVID-19].**




## 633 MENTAL HEALTH & ALCOHOL USE IN PEOPLE WITH & WITHOUT HIV BEFORE & DURING COVID-19

**Sara Bares**[1], Pamela May[1], Harlan Sayles[1], Renae Furl[1], Tony Wilson[2]
*[1]University of Nebraska Medical Center, Omaha, NE, USA, [2]Boys Town National Research Hospital, Omaha, NE*

**Background:** Increases in the prevalence of mental health symptoms during global pandemics have been observed. We hypothesized that people with HIV (PWH) and without HIV (HIV-) would experience an increase in mental health symptoms and alcohol use after the onset of the COVID-19 pandemic and that PWH would experience a greater increase than HIV- individuals.
**Methods:** Participants were recruited from two established cohorts of PWH and HIV- adults in Omaha, Nebraska for whom baseline data including mental health and alcohol use assessments had been collected prior to the pandemic. Participants were excluded from the original cohorts if they had any known psychiatric diagnosis or were taking antipsychotics or anticonvulsants. Participants were reassessed utilizing the Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), Alcohol Use Identification Test (AUDIT), and Pittsburgh Sleep Quality Index (PSQI) between February and April 2021. All outcomes were evaluated using generalized linear mixed models.
**Results:** Of the 95 participants who completed all questionnaires, 50 were PWH and 45 HIV -. Groups did not statistically differ in age, sex, race or ethnicity (mean: 45.67 years; 69.5% male; 74% non-Hispanic white). Pre-pandemic mean BDI-II, BAI, AUDIT and PSQI scores were higher in PWH versus HIV-. After the onset of the pandemic, mean BDI-II and AUDIT scores increased significantly in both groups (see Table; P<.001 and P=0.003, respectively) and AUDIT scores were significantly higher in males than females (P=.002). Measures of binge drinking and alcohol misuse as well as mean BAI and PSQI scores increased numerically intra-pandemic. Intra-pandemic mean BDI-II and AUDIT scores increased more among HIV- than PWH, but not significantly so. The percentage of PWH and HIV- participants who moved into a more severe category of depression as measured by the BDI-II (eg, from minimal to moderate) after the onset of the pandemic was identical (18%).
**Conclusion:** Measures of depression and alcohol use increased significantly after the onset of the COVID-19 pandemic in people with and without HIV. Although there were no significant differences in the changes between the groups, PWH had higher baseline scores so the increases in this group may have more clinical impacts. Screening for symptoms of mental health and alcohol use is critical, especially in PWH during a pandemic. Future work will explore the longer-term impact of the pandemic on mental health symptoms and alcohol use.

**Table. Measures of depression and alcohol use pre- and intra-pandemic**

| Depression | Pre-pandemic (0) vs Intra-pandemic (1) | | | | | |
|---|---|---|---|---|---|---|
| | All (0) | All (1) | PWH (0) | PWH (1) | HIV- (0) | HIV- (1) |
| BDI-II score, mean (sd) | 4.9 (5.3) | 7.1 (7.5) | 6.0 (6.2) | 8.0 (8.5) | 3.8 (3.9) | 6.2 (6.0) |
| Minimal to mild depression[a], n (%) | 91 (96) | 88 (93) | 46 (96) | 44 (88) | 45 (100) | 44 (98) |
| Moderate to severe depression[b], n (%) | 4 (4) | 7 (7) | 4 (8) | 6 (12) | 0 (0) | 1 (2) |
| **Alcohol use** | **Pre-pandemic (0) vs Intra-pandemic (1)** | | | | | |
| | All (0) | All (1) | PWH (0) | PWH (1) | HIV- (0) | HIV- (1) |
| AUDIT score, mean (sd) | 3.7 (3.1) | 4.3 (3.9) | 4.0 (3.7) | 4.9 (3.9) | 2.9 (2.8) | 3.7 (3.9) |
| Binge drinking[c], n (%) | 11 (12) | 14 (15) | 6 (12) | 9 (18) | 5 (11) | 5 (11) |
| Alcohol misuse[d], n (%) | 38 (40) | 49 (52) | 23 (46) | 28 (56) | 15 (33) | 21 (47) |

a. A score of ≤18 on the BDI-II
b. A score of >18 on the BDI-II
c. "Monthly or more" consumption 6 or more drinks on one occasion on the AUDIT tool
d. A score of ≥ 4 for males and ≥ 3 for females on the AUDIT tool

## 634 QUINOLINIC ACID IS A BIOMARKER OF COVID-19–ASSOCIATED COGNITIVE IMPAIRMENT

**Lucette A. Cysique**[1], Sophia Bracken[1], Yasmin Allen-Davidian[2], Benjamin Heng[2], Sharron Chow[2], Mona Dehhaghi[2], Ananda Staats Pires[2], David Darley[3], Anthony Byrne[3], Anthony Kelleher[4], Greg Dore[3], Gail Matthews[3], Gilles Guillemin[2], Bruce Brew[3]
*[1]University of New South Wales, Sydney, Australia, [2]Macquarie University, North Ryde, Australia, [3]St Vincent's Hospital, Sydney, Australia, [4]Kirby Institute, Sydney, Australia*

**Background:** COVID-19 infection-associated cognitive and olfaction impairments have an unclear pathogenesis, possibly related to systemic disease severity, hypoxia, or illness-associated anxiety and depression. A biomarker for these neurocognitive changes is lacking. The kynurenine pathway (KP) is an interferon stimulated myeloid cell mediated tryptophan degradation pathway important in immune tolerance, neurotoxicity and vascular injury, that is dysregulated in COVID-19. We hypothesized that neurocognitive impairments were associated with an activated KP.
**Methods:** The current analysis includes COVID-19 patients as part of the ADAPT study, a prospective cohort (St Vincent's Hospital Sydney, Australia). Disease severity was assessed with 18 acute symptoms and hospitalization status. Blood samples were taken 2 months (N=136) and 4 months (N=121) post diagnosis along with cognitive (Cogstate Computerized Battery, CBB; NIH toolbox Odor Identification Test, OIT) and mental health screenings (DMI-10; IESR, SPHERE-34 Psychological subscale grouped into a composite score). KP metabolites (PIC, QUIN, 3HK, 3HAA, AA, KYN, TRP, log for analyses except for TRP) were measured by GC-MS and uHPLC. The CBB and OIT data were demographically-corrected. CBB follow-up data was also corrected for practice effect. Linear mixed effect regression models with time effect (days post diagnosis) tested whether cognition, and olfaction were associated the KP (main and time interaction); while correcting for disease severity, mental health and comorbidities.
**Results:** 136 patients: mean age=46±15; 40% females; 90% English speaking background; disease severity: 40% mild, 50% moderate, 10% severe/ hospitalised; 34% treated comorbidities. At 2 months post diagnosis, 16% had cognitive impairment, and 25% had impaired olfaction. Cognitive impairment was more common in those with anosmia (p=.05). At 4 months, 23% had cognition impairment and 20% had impaired olfaction. QUIN (p=.001), 3HAA (p<.0001) increased over the study period, while TRP decreased (p=.02). QUIN level associated with poorer cognitive scores (p=.0007; QUIN (nM) between 800-1000 was most predictive). There was no time*QUIN interaction. QUIN association to cognition persisted when severe cases were excluded (p<.005).

**Conclusion:** COVID-19 is associated with KP activation, and the latter with cognitive impairment. QUIN was the only biomarker associated with cognitive impairment, and may be useful in monitoring and elucidating COVID-19 neuropathogenesis and treatment.

## 635 CSF AND BLOOD ANALYSES IN PARTICIPANTS WITH POST-COVID-19 NEUROPSYCHIATRIC SYMPTOMS

New Investigator Scholar

**Lindsay S. McAlpine**[1], Jennifer Chiarella[1], Hannah Walsh[1], Sharon Shin[1], Eunice Baik[1], Jennifer Yoon[1], Aroma Naeem[1], Michael Wilson[2], Samuel Pleasure[2], Christopher M. Bartley[2], Serena S. Spudich[1], Shelli F. Farhadian[1]
*[1]Yale University, New Haven, CT, USA, [2]University of California San Francisco, San Francisco, CA, USA*

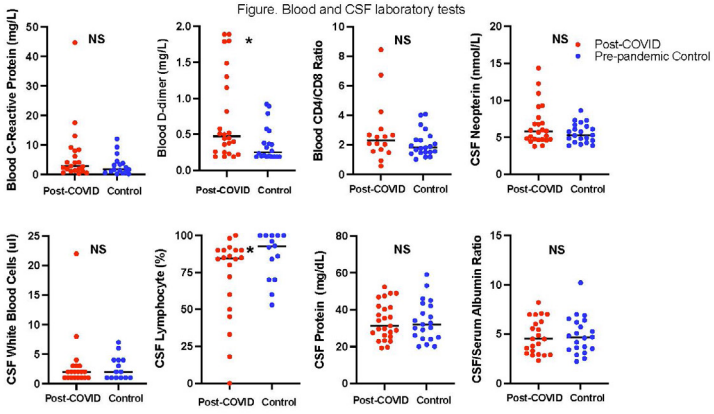
**Background:** The pathogenesis of neuropsychiatric symptoms persisting months after acute SARS-CoV-2 infection is poorly understood. We examined clinical and laboratory parameters in participants with post-acute COVID-19 neuropsychiatric symptom to assess for systemic and nervous system immune perturbations.

**Methods:** Participants with a history of laboratory confirmed COVID-19 and ongoing neurologic symptoms were enrolled in an observational study that collected medical history; detailed post-COVID symptom survey; and paired cerebrospinal fluid (CSF) and blood. In addition to standard clinical labs, neopterin and anti-SARS-CoV-2 antibodies (anti-spike, RBD, and nucleocapsid) were measured by ELISA. Non-parametric tests were used to compare CSF and blood findings between the post-COVID participants and pre-COVID-19 era healthy controls.

**Results:** Post-COVID participants (n=27) and controls (n=21) were similar in age (median 51 and 46 years), but there was a greater proportion of females (67% vs 24%; p=0.004) and white participants in the post-COVID cohort (63% vs 24%; p=0.04). The post-COVID study visit was a median of 264 days (IQR 59 – 332) after acute COVID-19 symptom onset. 35% were hospitalized during their acute illness; 12% required intensive care. 33% had previously been treated with medications for mental health conditions. The most frequent neuropsychiatric symptoms were cognitive impairment (67%), mood symptoms (67%), headache (56%), and neuropathy (41%). Blood c-reactive protein, T cell count, and T cell subset frequency (CD4% and CD8%) were similar between groups, while D-dimer was higher in the post-COVID cohort (median 0.48 vs 0.27 mg/L; p = 0.019) (Figure). CSF WBC, protein, neopterin, and CSF/blood albumin ratio were similar between the groups; the frequency of CSF lymphocytes was lower in the post-COVID cohort (p = 0.05) (Figure 1). Antibodies against at least one SARS-CoV-2 antigen were detected in 7/10 CSF and 8/9 blood samples in the post-COVID CSF (antibody reactivity range 1.5 to 55-fold greater than to control antigens).

**Conclusion:** In this small cohort of post-COVID participants with neurologic symptoms, we found limited differences in CSF and blood markers when compared to pre-pandemic healthy controls. Deeper immunophenotyping in a larger number of participants may provide greater insight into subtle differences. The presence of anti-SARS-CoV-2 antibodies in CSF months after acute infection warrants further investigation.

Figure. Blood and CSF laboratory tests




## 636 TOCILIZUMAB (BIOSIMILAR) USE IN CYTOKINE STORM OF SEVERE COVID-19 PNEUMONIA

Late Breaking

**Nagalingeswaran Kumarasamy**[1], Sawardekar Vinayak Maruti[2], Sanjiv Maheshwari[3], Anand Nikalje[4], Chirag C. Rathod[5], Dr. Manish K.Jain[6], Ashish Goyal[7], Naveen Chander Reddy Podduturi[8], Archana Gautam[9], Shubhadeep Sinha[10], Sreenivasa Chary Sriramadasu[10], Bala Reddy Bheema Reddy[11], Sheejith Kakkunnath[10], Pankaj Thakur[10], Leela Talluri[10]
*[1]VHS Infectious Diseases Medical Centre, Chennai, India, [2]St George's Hospital, Mumbai, India, [3]Jawahar Lal Nehru Medical College, Ajmer, India, [4]Mahatma Gandhi Mission's Medical College and Hospital, Aurangabad, India, [5]GMERS Medical College & Hospital, Vadodara, India, [6]Maharaja Agrasen Superspeciality Hospital, Jaipur, India, [7]Orchid Hospital, Pune, India, [8]AIG Hospitals, Hyderabad, India, [9]Krishna Institute of Medical Sciences, Satara, India, [10]Hetero Labs Limited, Hyderabad, India, [11]Hetero Biopharma Limited, Jedcherla, India*

**Background:** Tocilizumab is an IgG1 class humanized monoclonal antibody targeting IL-6 receptor (IL-6R). IL-6 is a key cytokine involved in cytokine storm of severe COVID-19. Tocilizumab down-regulates IL-6 preventing fatal and permanent damage to vital organs, significantly preventing COVID-19 related mortality and morbidity. Therefore, this study aimed to compare the efficacy and safety of Tocilizumab (biosimilar) developed by Hetero Biopharma Ltd, India vs reference medicinal product (RMP)-Tocilizumab manufactured by Roche in cytokine storm of severe COVID-19 pneumonia.

**Methods:** This multicenter, randomized, double-blind, active-controlled study enrolled patients aged 18 to 65 years, with laboratory-confirmed, hospitalized, severe COVID-19 disease with elevated inflammatory markers not on mechanical ventilation. Patients were randomized (3:1 ratio) to receive either Test-Tocilizumab (Test) 8 mg/kg or RMP-Tocilizumab 8mg/kg, maximum 800mg, administered once on day 1. The primary endpoint was the cumulative proportion of patients requiring mechanical ventilation by Day 14. Secondary endpoints included 28 day mortality rate, proportion of patients with a 2-point decrease in WHO ordinal scale, time to clinical failure (death or required mechanical ventilation or withdrawn), change in inflammatory markers (CRP, IL-6, Ferritin and D-dimer) and duration of hospital stay in days. Safety endpoints included the incidence of adverse events; the proportion of patients discontinued the study due to adverse events and the incidence of any post-treatment bacterial and/or fungal infection.

**Results:** Out of 211 patients screened, 172 patients were randomized (131 to Test and 41 to RMP) to receive Tocilizumab 8mg/kg. Patients were similar in both groups at baseline in terms of age, gender, weight etc. Fourteen (10.69%) patients in Test and 5 (12.20%) patients in RMP progressed to mechanical ventilation by Day 14 (p=0.7789). Overall, 9 (7.83%) patients died in Test vs 5 (13.16%) in RMP during 28 days follow up (p=0.3382). Clinical improvement was seen 62.60% and 77.10% vs 53.66% and 73.17% in Test vs RMP at day 14 and 28 respectively. The time to clinical failure was 6 vs 5 days and time to clinical improvement was 11 vs 11.5 days. Hospitalization duration was 12.9 versus 13.8 days in the Test and RMP. ARDS, Insomnia and Pain were most commonly reported adverse events.

**Conclusion:** Tocilizumab biosimilar is comparable with RMP-Tocilizumab in preventing mechanical ventilation in severe COVID19 pneumonia patients

## 637 THE IMPACT OF COVID-19 TREATMENTS ON PATIENT OUTCOMES: A PROBABILISTIC VIEW

**Bradley S. Price**[1], Maryam Khodaverdi[1], Hamidreza Moradi[2], H Timothy Bunnell[3], J Zachary Porterfield[4], Michael T. Vest5, Susan L. Santangelo[6], Wesley Kimble[1], Alfred [1]. Anzalone[7], Jeremy Harper[8], Sally L. Hodder[1]
*[1]West Virginia Clinical and Translational Science Institute, Morgantown, WV, USA, [2]University of Mississippi Medical Center, Jackson, MS, USA, [3]Nemour's Children's Health, Wilmington, DE, USA, [4]University of Kentucky, Lexington, KY, USA, [5]Christiana Care Health System, Newark, DE, USA, [6]Tufts University, Boston, MA, USA, [7]University of Nebraska Medical Center, Omaha, NE, USA, [8]Owl Health Works LLC, Indianapolis, IN, USA*

**Background:** The World Health Organization (WHO) ordinal scale (OS) is used to evaluate participant outcomes in clinical trials. We modified the WHO OS to enable assessment of patient outcomes associated with various treatment agents using the National COVID Cohort Collaborative (N3C), a national database containing electronic Health Record (EHR) data from > 2.7 million persons with a COVID-19 diagnosis from > 55 U.S. sites.

**Methods:** Modified OS severity scores (Table 1) were assigned in the first through fourth weeks following COVID-19 diagnosis for a sample of patients

in N3C. To adjust for disease severity at patient hospitalization, we developed separate models to examine OS levels of 3, 5, 7, and 9. Elastic net penalized multinomial logistic regression was used to simultaneously identify risk factors and predict the probability of each level of the ordinal scale at week 4. We studied groups of anticoagulants (AC), steroids, antibiotics, antiviral agents (AA), monoclonal antibodies (MA), and a miscellaneous group that included all other treatments. Other factors considered were presence of comorbid conditions using the Charlson Comorbidity Index (CCI), ethnicity, age, gender, and time of diagnosis (by quarter).

**Results:** We included 1,489,191 COVID-19 (161,385 outpatients were excluded) patients. Patient characteristics and treatment approaches applied to each OS level were analyzed (Table 1). For hospitalized patients with a Week 1 OS score of 3,5,7, or 9, we found that increased CCI values are associated with higher probabilities of a worsened OS score at Week 4. Given that MAs are a standard treatment for patients at OS levels 3 and 5, and that steroids are typically used at OS 7 and 9, we studied treatment combinations related to MA and steroids given during Week 1. Improved outcomes by Week 4 were demonstrated with AA+MA for OS 3 and for AC+MA for OS 5 (Table 1). Patients at OS 7 in Week 1 had improved Week 4 outcomes with steroids alone while OS 7 patients with CCI>10 had better outcomes with steroids+AC. OS 9 patients treated with steroids+MA had better outcomes compared with those not given that combination.

**Conclusion:** Our analyses identify relationships between COVID-19 serverity, specific treatments and outcomes at 4 weeks after diagnosis. Use of MA at lower levels of severity, and steroids at higher severity levels were associated with survival to hospital discharge.

**Table 1. Treatments Associated with Highest Probability of Hospital Discharge by Week 4**

| Modified Ordinal Scale Score at Week 1 of COVID-19 | Definition | Week 1 Sample Size | Treatment with Highest Probability of Week 4 Hospital Discharge |
|---|---|---|---|
| OS 3 | Hospitalized | 1,230,702 | Antiviral Agents with Monoclonal Antibodies |
| OS 5 | Hospitalized with Oxygen | 23,329 | Anticoagulants with Monoclonal Antibodies |
| OS 7 | Hospitalized on Ventilator | 9,644 | CCI<10: Steroids Only<br>CCI>10: Steroids and Anticoagulants |
| OS 9 | Hospitalized on ECMO | 15,516 | Steroids with Monoclonal Antibodies |

## 638 ALTERED GUT MICROBIOTA AND RESPIRATORY DYSFUNCTION 3 MONTHS AFTER SEVERE COVID-19

**Beate Vestad**[1], Thor Ueland[1], Tøri V. Lerum[1], Tuva B. Dahl[1], Kristian Holm[1], Andreas Barratt-Due[1], Anne Ma Dyrhol-Riise[1], Birgitte Stiksrud[1], Hedda B. Hoel[1], Bente Halvorsen[1], Annika E. Michelsen[1], Ole H. Skjønsberg[1], Pål Aukrust[1], Johannes R. Hov[1], Marius Trøseid[1]

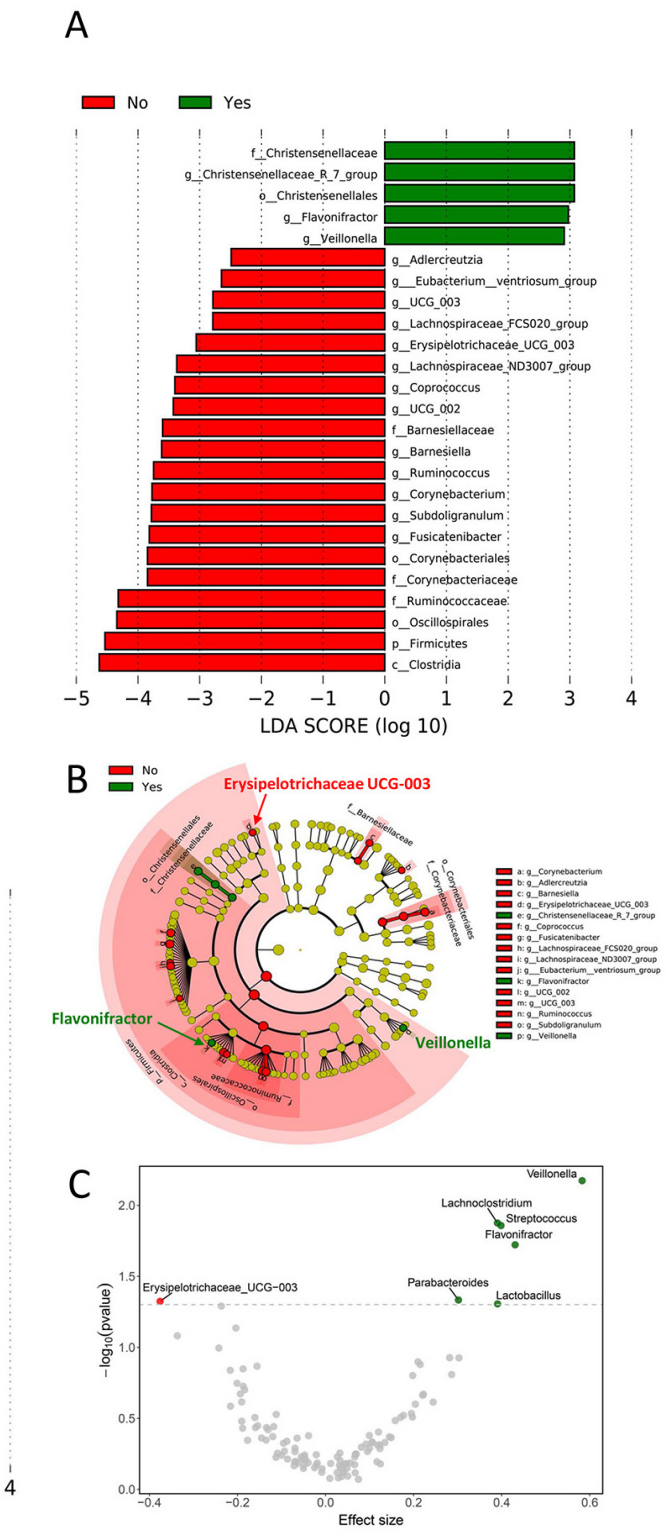
*[1]Oslo University Hospital, Oslo, Norway*

**Background:** Although COVID-19 is primarily a respiratory infection, mounting evidence suggests that the GI tract is involved in the disease, with gut barrier dysfunction and gut microbiota alterations being related to disease severity. Whether these alterations persist and associate with long-term respiratory dysfunction is unknown.

**Methods:** From the NOR-Solidarity trial (n=181), plasma was collected during hospital admission and after three months, and analyzed for markers of gut barrier dysfunction and inflammation. At the three-month follow-up, pulmonary function was assessed by measuring diffusing capacity of the lungs for carbon monoxide (DLCO), and rectal swabs for gut microbiota analyses were collected (n= 97) and analysed by sequencing of the 16S rRNA gene.

**Results:** Gut microbiota diversity was reduced in COVID-19 patients with respiratory dysfunction, defined as DLCO below lower limit of normal three months after hospitalization. These patients also had an altered global gut microbiota composition (Fig. 1), with reduced abundance of Erysipelotrichaceae UCG-003 and increased abundance of Flavonifractor and Veillonella, the latter potentially being linked to fibrosis. During hospitalization, increased plasma levels of lipopolysaccharide-binding protein (LBP) were strongly associated with respiratory failure, defined as pO2/fiO2-(P/F-ratio)<26.6 kPa. LBP levels remained elevated during and after hospitalization, and were associated with low-grade inflammation and respiratory dysfunction after three months. Figure 1 legend: Gut microbial composition in patients with respiratory dysfunction at the three-month follow-up (DLCO<="" div="">

**Conclusion:** Respiratory dysfunction after COVID-19 is associated with reduced biodiversity and gut microbiota alterations, along with persistently elevated LBP levels. Our results point to a potential gut-lung axis that should be further investigated in relation to long-term pulmonary dysfunction and long COVID.




## 639 CAPSULE ENDOSCOPY FINDINGS IN PATIENTS WITH SEVERE SARS-CoV-2 INFECTION: PILOT STUDY

**Daniela Garrido-Rodriguez[1],** Fernanda Torres-Ruiz[1], Gerardo Blanco-Velasco[2], Amy B. Peralta-Prado[1], Isabel León-Rodríguez1, Julio C. Lara-Muñoz[1], William C. Lara-Vazquez[1], Dulce M. López-Sánchez[1], Gonzalo Salgado Montes de Oca[1], Santiago Ávila-Ríos[1]

*[1]National Institute of Respiratory Diseases, Mexico City, Mexico, [2]Instituto Mexicano del Seguro Social, Centro Médico Nacional Siglo XXI, Mexico City, Mexico*

**Background:** Although SARS-CoV-2 has mainly respiratory manifestations, gastrointestinal symptoms are observed in 30% of cases. The ACE-2 receptor

used by SARS-CoV-2 to infect cells is highly expressed in the brush border of enterocytes. However, studying the small intestine in live patients is a challenge in the field of clinical research. A minimally invasive alternative for studying the small intestine is the use of capsule endoscopy, which could be useful in the context of COVID-19. Here, we describe endoscopic changes in the mucosa of the small intestine secondary to severe SARS-CoV-2 infection in hospitalized patients.

**Methods:** We performed a prospective observational study in hospitalized patients with a severe COVID-19 according to NIH guidelines. Participants with a positive COVID-19 PCR from nasopharyngeal swab, hemodynamically stable, able to swallow, and without additional respiratory co-infections, were enrolled between January 27th and May 17th, 2021 at the largest tertiary COVID-19 referral center in Mexico City. Demographic and clinical characteristics were collected for each participant from clinical files. A PillCam capsule from Medtronic® was used for Capsule Endoscopy (CE). Each capsule study was reviewed separately by two trained endoscopists. Detection of SARS-CoV-2 RNA in stool samples was performed according to CDC guidelines for all participants.

**Results:** Twenty volunteers were enrolled in the study. Diarrhea was the most common gastrointestinal symptom (78%). CE study was normal in 6 participants, while the rest showed at least one intestinal finding. The most frequent finding was shortening or atrophy of villi and hyperemia (45%); followed by red spots (40%), and ulcers (15%). Two participants with shortening or atrophy of villi also presented denuded mucosa. CE findings were observed mainly in duodenum and jejunum. Participants showing changes in villi also presented positive SARS-CoV-2 RNA in stool.

**Conclusion:** We observed that macroscopic changes in the small intestine mucosa, specifically in villi, occurred frequently in severe COVID-19 patients. These changes were accompanied by the presence of SARS-CoV-2 RNA in stool. We proposed the term COVID-19 Enteropathy to encompass these findings. Further studies are warranted to establish mechanisms of SARS-CoV-2-associated gastrointestinal disease.

## 640 HIV AND SARS-CoV-2 INFECTION AND OUTCOMES IN THE MID-ATLANTIC US

**Amanda B. Spence**[1], Sameer Desale[2], Jennifer Lee[1], Princy N. Kumar[1], Xu Huang[2], Stanley E. Cooper[1], Stephen Fernandez[2], Seble Kassaye[1]
*[1]Georgetown University Medical Center, Washington, DC, USA, [2]MedStar Health Research Institute, Hyattsville, MD, USA*

**Background:** Reports of severity of illness and outcomes of SARS-CoV-2 infection in persons living with HIV (PLWH) vary across cohorts. Limited data exists regarding post-infection complications among PLWH.

**Methods:** We examined the clinical characteristics and outcomes among PLWH infected with SARS-CoV-2 compared to an age and race matched cohort in a healthcare system composed of ten academic and community-based hospitals in the mid-Atlantic United States. Descriptive statistics were used and multivariate logistic regression analyses were performed to explore factors associated with incident hospitalization and death/mechanical ventilation among PLWH.

**Results:** Between March 2020 and November 2020, 281 d PLWH were diagnosed with SARS-CoV-2 infection among 1632 tested. The mean age was 51.5 years (SD: 12.74), 63% (n=177) were male, and 86% (n=237) were African-American/Black. The median CD4+ T lymphocyte count was 623 cells/$mm_3$ [383, 938] and 87% had a HIV viral load <200 copies/mL. More PLWH were hospitalized than age/sex matched HIV-seronegative controls, 47% (n=132/281) versus 24% (n=269/1124), (p<0.001). Rates of post-Coronavirus Disease 2019 (COVID-19) cardiovascular, thrombotic, acute kidney injury, and concurrent infections were similar between PLWH and HIV-seronegative individuals. All cause mortality was similar between PLWH and HIV-seronegative individuals, 14% versus 13% (p=0.75). In adjusted analyses, hospitalization among PLWH with COVID-19 was associated with older age aOR 1.03 (95% CI 1.03, 1.06, p=0.022) and Medicaid insurance aOR 2.87 (95% CI 1.45, 5.78, p=0.003).

**Conclusion:** In an age/sex matched cohort, PLWH with well-controlled HIV and SARS-CoV-2 infection had higher rates of hospitalization but similar mortality rates compared with HIV-seronegative individuals. Despite higher rates of hospitalization and higher comorbidity burden, rates of post-COVID-19 events were similar. However, older age and Medicaid insurance status associated with more severe disease among PLWH suggesting the importance of targeted interventions to mitigate the effects of modifiable inequities.

## 641 USE OF CORTICOSTEROIDS TO MANAGE HOSPITALIZED PATIENTS WITH COVID-19 IN ZAMBIA

**Peter Minchella**[1], Sombo Fwoloshi[2], Duncan Chanda[2], Davies Kampamba[2], Megumi Itoh[1], Khozya D. Zyambo[2], Jonas Hines[1], Suilanji Sivile[2], Simon Agolory[1], Lloyd B. Mulenga[2]
*[1]Centers for Disease Control and Prevention, Lusaka, Zambia, [2]Ministry of Health, Lusaka, Zambia*

**Background:** Corticosteroids are recommended for management of patients with severe COVID-19 who require supplemental oxygen. Despite limited evidence on their benefits in sub-Saharan Africa, corticosteroids were adopted as part of COVID-19 management guidelines by many African countries, including Zambia. We report on the use of corticosteroids and related clinical outcomes among hospitalized patients in Zambia.

**Methods:** Patients with SARS-CoV-2 infection who were admitted in one of nine COVID-19 treatment centers across Zambia between March 2020 and September 2021 were included. Patient demographic and clinical information were collected, including corticosteroid use and in-patient disposition (discharged or died). Severe COVID-19 at admission was defined as having an oxygen saturation <90%, respiratory rate >30 breaths/minute, or a need for oxygen therapy. Primary outcomes for the study were prolonged hospitalization (i.e., ≥5 days in the treatment center among patients who were discharged) and in-hospital mortality. We used mixed-effects logistic regression to assess associations between corticosteroid use and primary outcomes among patients with severe COVID-19 at admission. Models were adjusted for age, sex, number of comorbid conditions, and COVID-19 treatment center.

**Results:** The study included 2,630 patients, 1,751 (67%) of whom had severe COVID-19 at admission. Of those, 1,587 (91%) received corticosteroids with 1,470 (93%) initiating at or before treatment center admission. The median duration of treatment with corticosteroids was 3 days (interquartile range: 1 – 6) and 95% of patients received dexamethasone. Regression analyses indicated that receiving corticosteroids was associated with prolonged hospitalization for discharged patients (adjusted odds ratio (aOR): 2.98; 95% confidence interval (CI): 1.78 – 5.22), but not with in-hospital mortality (aOR: 1.14; 95% CI: 0.76 – 1.75)).

**Conclusion:** Use of corticosteroids was common among admitted patients with severe COVID-19, but not associated with improved COVID-19 outcomes. While our study was not designed to assess the effectiveness of corticosteroids, these results suggest a need to both comprehensively assess their use relative to national guidelines and investigate their benefits in the African context. Important differences in epidemiology and healthcare system capacity could modify the effect of corticosteroids in Zambia relative to countries where the evidence for their use was generated.

**Demographic and clinical characteristics of patients admitted to COVID-19 treatment centers with severe COVID-19 (N = 1751) * by whether they received corticosteroids– Zambia, March 2020 – September 2021**

| | No. (%) | | |
|---|---|---|---|
| demographic/clinical/outcome | corticosteroids (n=1587) † | no corticosteroids (n=164) † | p-value§ |
| male sex | 1005/1580 (64) | 101 (62) | 0.67 |
| mean age, years (SD) | 56.2 (15.8) | 53.1 (20.1) | 0.066 |
| Age ≥60 years | 698/1569 (45) | 64/162 (40) | 0.26 |
| hypertension | 817/1504 (54) | 81/157 (52) | 0.57 |
| diabetes | 367/1472 (25) | 38/156 (24) | 0.95 |
| ≥3 comorbid conditions¶ | 205 (13) | 24 (15) | 0.62 |
| median days in treatment center (IQR) | 4 (2 – 6) | 2 (1 – 3) | <0.001 |
| in-hospital death | 451/1490 (30) | 42/145 (29) | 0.81 |

Abbreviations: SD = standard deviation; IQR = interquartile range

*Reported as number (%) unless indicated otherwise.

†Denominator is equal to n unless noted otherwise. Cases in which the denominator was less than n are due to missing data.

§P-values <0.05 were considered statistically significant. Comparison of proportions was via chi-square test and comparison of non-normally distributed variables was via Wilcoxon test. The tests used did not account for site-level clustering. P-value for three or more comorbidities is for a binary variable (less than three versus three or more comorbidities)

¶Comorbid conditions composite term is based on the number of self-reported comorbidities. Eligible comorbidities included chronic cardiac disease, hypertension, pulmonary disease, active TB, previous TB, asthma, kidney disease, liver disease, neurologic disorder, diabetes, current smoking, asplenia, and malignant neoplasm. Conditions commonly linked to COVID-19 mortality (diabetes and hypertension) are listed in the table.

## 642 VARIABLES ASSOCIATED WITH HOSPITALIZATION DUE TO COVID-19 IN PEOPLE LIVING WITH HIV

**Fernanda Rombini**[1], Jamile Ballivian[2], Diego Cecchini[1], Liliana Calanni[3], Fabricio Morales[4], Elena Obieta[5], Laura Morganti[6], Claudia Migazzi[7], Maria L. Yantorno[8], Maria Marta Greco[8], Rosana Cuini[9], Martin Hojman[10], Diana Pinto[1], Isabel Cassetti[1]
*[1]Helios Salud, Buenos Aires, Argentina, [2]Hospital Moyano, Buenos Aires, Argentina, [3]CEIN Unidad Infectológica Neuquén, Neuquen, Argentina, [4]Sanatorio Anchorena, Buenos Aires, Argentina, [5]Hospital Municipal Ciudad de Boulogne, Boulogne,*

*Argentina, [6]Hospital General de Agudos Cosme Argerich, Buenos Aires, Argentina, [7]Hospital General de Agudos Presidente Perón de Avellaneda, Avellaneda, Argentina, [8]Hospital Español de La Plata, La Plata, Argentina, [9]Hospital General de Agudos Dr. Teodoro Álvarez, Buenos Aires, Argentina, [10]Hospital General de Agudos Bernardino Rivadavia, Buenos Aires, Argentina*

**Background:** Argentina has been one of the most affected countries by the COVID-19 pandemic, however, there are limited data regarding evolution of people living with HIV (PLWH) infected with SARS-CoV-2. This study evaluates characteristics associated with hospital admission due to COVID-19 among PLWH in Argentina.

**Methods:** Adult PLWH with confirmed SARS-CoV-2 infection were enrolled in a prospective observational multicentric cohort study to evaluate hospitalization due to COVID-19. Participating centers included nationwide HIV clinics and general hospitals from Argentina. A multivariable logistic regression model was performed to identify variables associated with hospitalization due to COVID-19.

**Results:** Of 844 PLWH enrolled, 21.8% required hospital admission due to COVID-19. Characteristics of PLWH with and without hospitalization are shown in table 1. On a multivariable logistic regression model, age>=60 and presence of other comorbidities were associated with admission (OR: 1.82; 95%CI:1.07-3.11; p<0.028; OR: 1.73; 95%CI: 1.22- 2.46 p<0.002; respectively). Female sex and CD4+ count >=500 cells/ml (OR: 0.60;95%CI:0.41-0.87;p=0.008; and OR:0.30; 95% CI:0.14-0.66;p=0.003; respectively) were inversely associated with admission. ART and detectable viral load had no impact on hospitalization.

**Conclusion:** We provide the first analysis regarding variables associated with hospitalization among PLWH in Argentina. Hospitalization in this population was associated with traditional risk factors (age, comorbidities) without influence of ART and viral load. According to our study, female sex and high CD4+ T-cell count provide a significant reduction in the risk of admission to hospital.

**Table.1 Characteristics of PLHIV with and without hospital admission due to COVID-19 in Argentina**

| Variables | | Total N=844 | Not required admission N=660 | Required Admission N=184 |
|---|---|---|---|---|
| Age categories | Age<60 | 772 (91.5%) | 614 (93.0%) | 158 (85.9%) |
| | Age>=60 | 72 (8.5%) | 46 (7.0%) | 26 (14.1%) |
| Sex | Male | 552 (65.4%) | 417 (63.2%) | 135 (73.4%) |
| | Female | 292 (34.6%) | 243 (36.8%) | 49 (26.6%) |
| Viral load | <20 copies/ml | 571 (67.7%) | 447 (67.7%) | 124 (67.4%) |
| | >=20copies/ml | 273 (32.3%) | 213 (32.3%) | 60 (32.6%) |
| CD4+ categories | CD4<200 cells/ml | 32 (3.8%) | 17 (2.6%) | 15 (8.2%) |
| | CD4 200-449 cells/ml | 202 (23.9%) | 145 (22.0%) | 57 (31.0%) |
| | CD4 >=500 cells/ml | 610 (72.3%) | 498 (75.5%) | 112 (60.8%) |
| Other comorbidities | No | 568 (67.3%) | 463 (70.2%) | 105 (57.1%) |
| | Yes | 276 (32.7%) | 197 (29.8%) | 79 (42.9%) |
| Under ART at COVID-19 diagnosis | No | 130 (15.4%) | 94 (14.2%) | 36 (19.6%) |
| | Yes | 714 (84.6%) | 566 (85.8%) | 148 (80.4%) |

## 643 ZINC DEFICIENCY IS INDEPENDENTLY ASSOCIATED WITH INCREASED COVID-19 DISEASE SEVERITY

New Investigator Scholar

**Christian F. Mouchati**[1], Sokratis N. Zisis[1], Jared C. Durieux[2], Sarah Scott[2], Beth Smith[2], Danielle Labbato[2], Grace A. McComsey[1]

*[1]Case Western Reserve University, Cleveland, OH, USA, [2]University Hospitals Cleveland Medical Center, Cleveland, OH, USA*

**Background:** COVID-19 has the most impact on people with comorbidities likely due to a higher inflammatory state. Zinc (Zn) is known for its substantial involvement in immune response as an antioxidant and anti-inflammatory agent. Zn plasma levels' clinical significance at COVID diagnosis is not yet established. We investigated the effects of Zn deficiency and inflammation on COVID-19 outcomes.

**Methods:** Plasma Zn levels were collected from patients during the acute phase of a confirmed COVID-19 diagnosis. Data was dichotomized into Zn deficient (Zn<75 µg/dL) and Zn sufficient (Zn ≥75 µg/dL). Soluble tumor necrosis factor alpha receptor II (sTNF-RII) and intestinal fatty-acid binding protein (I-FABP) were also measured. COVID-19 outcomes were classified according to the WHO clinical progression scale (0-10), then stratified into 3 groups [grp 1= (WHO score 0-4) asymptomatic or mild disease; moderate grp 2= (WHO 5-6), and severe grp 3= (7-10)]. Hazard ratios (AHRs) and 95% Confidence Intervals (CIs) were computed using cumulative logit regression and adjusted for demographics, BMI, comorbidities, inflammation markers, and laboratory data.

**Results:** We included 149 patients with a confirmed COVID-19 diagnosis. The median age (interquartile range [IQR]) was 53 years (38.0, 63.0); 42% of the patients were female, 52% non-white, and 86% had at least one comorbidity. Overall, 50% of patients were in grp 1= asymptomatic or mild, whereas 8.5% had the worse outcome (grp 3). More than half of the participants (54%) had sufficient zinc levels. There was not enough evidence to suggest any differences regarding age, gender, body mass index (BMI), hemoglobin, white blood cells, transaminases enzymes, I-FABP, and sTNF-RII between the Zn- sufficient and deficient arms (p>0.05). However, 21% of the Zn sufficient arm were non-White compared to 31% in the deficient arm (p= 0.0004). Patients with zinc deficiency had a median BMI of 31.96 kg/$m_2$ (IQR: 26.69, 36.44) and a median sTNF-RII of 3027.00 (IQR: 2446.00, 4468.00). In adjusted models, as zinc levels decreased, the risk of severe COVID-19 outcomes increased [AHR: 0.24 (95% CI: 0.06, 0.93)]. As sTNF-RII increases, but not I-FABP, the risk of severe COVID-19 outcomes rises two-fold [AHR: 2.17 (95% CI: 1.10, 4.31)].

**Conclusion:** Zinc deficiency and higher levels of sTNF-RII during acute COVID-19 presentation are independently associated with worse outcomes, suggesting a potential relationship between these 2 variables in COVID-19 progression.

**Table 1. Hazard Ratios* and 95% Confidence Intervals (CIs)**

| | COVID-19 Outcome | | p-value |
|---|---|---|---|
| | UHR (95% CI) | AHR (95% CI) | |
| Zinc ng/mL** | 0.11 (0.04, 0.28) | 0.24 (0.06, 0.92) | 0.037 |
| Age (years)*** | 2.47 (1.47, 4.16) | 3.63 (1.34, 9.83) | 0.01 |
| Female | 1.04 (0.66, 1.63) | 1.30 (0.67, 2.52) | 0.44 |
| non-White | 3.83 (2.30, 6.40) | 2.66 (1.27, 5.57) | 0.01 |
| Comorbidities (Any) | 5.92 (1.85, 18.89) | 1.62 (0.35, 7.52) | 0.54 |
| sTNF-RII** | 4.08 (2.17, 7.66) | 2.17 (1.10, 4.31) | 0.026 |

** UHR=Unadjusted Hazard Ratio; AHR=Adjusted Hazard Ratio*
*** Natural log-transformed*
**** Log(base)2 transformed*

## 644 MENSTRUATION IRREGULARITIES AMONG REPRODUCTIVE-AGE WOMEN DURING THE COVID-19 PANDEMIC

**Emily M. Cherenack**[1], Ana S. Salazar[1], Patricia Raccamarich[1], Violeta J. Rodriguez[2], Alejandro Mantero[1], Sophia F. Gerard[1], Marissa Maddalon[1], Deborah Jones Weiss[1], Nichole R. Klatt[3], Maria L. Alcaide[1]

*[1]University of Miami, Miami, FL, USA, [2]University of Georgia, Athens, GA, USA, [3]University of Minnesota, Minneapolis, MN, USA*

**Background:** Women have reported increased menstrual irregularities during the COVID-19 pandemic. It is unknown if this is due to biological (i.e., the effect of SARS-CoV-2 infection or vaccination) and/or psychosocial factors. This study examined menstrual irregularities during the COVID-19 pandemic and the association of abnormal menses with the presence of SARS-CoV-2 antibodies, stress, and mental health among reproductive age women.

**Methods:** A cross-sectional study of 182 HIV-negative, sexually active, 18- to 45-year-old cisgender women was conducted on biobehavioral factors influencing HIV risk. From January 2019 to September 2021, participants completed a survey of menstrual irregularities over the previous three months, previous month condomless vaginal intercourse, and plans to conceive. Starting October 2020, SARS-CoV-2 IgG antibodies were measured using an FDA EUA rapid test assay using whole blood, and participants completed the Centers for Epidemiological Studies Depression Scale, the Loneliness Brief Form, the Perceived Stress Scale. History of COVID-19 vaccination was self-reported. Menstrual irregularities were compared by recruitment date (pre-pandemic vs. during pandemic/after April 2020) and by IgG antibody status. Logistic regression models tested if the presence of antibodies was associated with menstrual irregularities when controlling for age (in all models) and stress, depression, and loneliness in separate models.

**Results:** Key variables are illustrated in Table 1. Menstrual irregularities did not differ by enrollment date. About half of women (n=36) had detectable IgG; 5 had been vaccinated. Controlling for age, women with detectable IgG had 7.3, 95% CI [1.5, 36.5], times the odds of menstrual irregularities. Neither age, stress, nor mental health were associated with irregular menstruation. Among unvaccinated women (n=31), 35% with IgG antibodies had irregular menstruation compared to 0% without IgG antibodies. Among women with no plans to conceive, 74% had condomless intercourse, of whom 11% had irregular menstruation.

**Conclusion:** Findings suggest a relationship between SARS-CoV-2 infection and irregular menstruation that was not accounted for by stress or mental health. During the COVID-19 pandemic, increased condom use and routine pregnancy testing may be merited among women not intending to conceive.

Table 1
Sociodemographics, SARS-CoV-2 IgG antibodies, history of COVID-19 vaccination, and associations between key variables and irregular menstruation (chi-square)

| | |
|---|---|
| **Age** (*n* = 182) | *M* = 33 (*SD* = 8) |
| **Race** (*n* = 182) | *n* (%) |
| Black | 108 (59) |
| White | 60 (33) |
| Asian | 2 (1) |
| Other | 12 (7) |
| **Ethnicity** (*n* = 182) | |
| Hispanic | 55 (30) |
| Non-Hispanic | 94 (52) |
| Haitian | 7 (4) |
| Other | 26 (14) |
| **SARS-CoV-2 IgG Antibodies** (*n* = 73) | |
| Detectable IgG | 37 (51) |
| Undetectable IgG | 36 (49) |
| **COVID-19 Vaccination** (*n* = 36) | |
| Vaccinated (at least 1 dose) | 5 (14) |
| Unvaccinated | 31 (86) |
| **Irregular Menstruation** (*N* = 182) | 25 (13) |

| Chi-Square Comparisons of Irregular Menstruation | *n* with Irregular Menstruation (%) | $X^2$ p-value |
|---|---|---|
| **By recruitment date** (*N* = 182) | | .192 |
| Pre-pandemic (*n* = 109) | 12 (11) | |
| During pandemic (*n* = 73) | 13 (18) | |
| **By antibody status** (*N* = 73) | | .005 |
| Detectable IgG (*n* = 37) | 2 (5) | |
| Undetectable IgG (n = 36) | 11 (31) | |
| **By antibody status, unvaccinated only** (*N* = 31) | | .026 |
| Detectable IgG (*n* = 20) | 7 (35) | |
| Undetectable IgG (*n* = 11) | 0 (0) | |

## 645 CRISPR-DETECTED CELL-FREE DNA FOR PEDIATRIC TB DIAGNOSIS AND TREATMENT RESPONSE

**Sylvia LaCourse**[1], Zhen Huang[2], Joshua Stern[1], Jaclyn Escudero[1], Lisa Marie Cranmer[3], Irene Njuguna[4], Elizabeth Maleche-Obimbo[5], Dalton C. Wamalwa[5], Christopher Lyon[2], Grace John-Stewart[1], Tony Hu[2]

*[1]University of Washington, Seattle, WA, USA, [2]Tulane University, Metairie, LA, USA, [3]Emory University, Atlanta, GA, USA, [4]Kenyatta National Hospital, Nairobi, Kenya, [5]University of Nairobi, Nairobi, Kenya*

**Background:** Children with HIV (CHIV) are at high risk for tuberculosis (TB)-related morbidity and mortality but often missed by sputum-based assays. We developed a CRISPR-based TB assay (CRISPR-TB) that detects an M. tuberculosis (Mtb)-specific multicopy insertion element (IS6110) in cell-free DNA (cfDNA) isolated from 200µl serum samples.

**Methods:** We evaluated CRISPR-TB performance using cryopreserved serum from hospitalized CHIV enrolled in an ART timing trial in Kenya (NCT02063880) who underwent TB evaluation, including Xpert and culture of sputum/gastric aspirates and stool Xpert. Serum was collected at baseline, 2, 4, 12, and 24 weeks. Children were post-hoc classified per NIH pediatric TB criteria as: confirmed (Xpert and/or culture positive), unconfirmed (≥2 positive criteria: TB signs/symptoms, CXR, TB exposure or positive tuberculin skin test, or TB treatment response), or unlikely TB.

**Results:** Among 153 children with evaluable samples, 48% were female, median age was 2.0 years (IQR 0.8-5.1), 68% were severely immunosuppressed, and 18% died. These children were classified post-hoc as confirmed (8%; 13), unconfirmed (42%; 153), and unlikely TB (49%; 75); 58 (38%) initiated TB treatment. CRISPR-TB sensitivity was 100% (95%CI 75.3-100) for confirmed TB and detected an 80% (52/65) of children with unconfirmed TB, including 84.8% [95%CI 71.1-93.7] with unconfirmed TB who initiated TB treatment (Table). Specificity was 50.7% (95%CI 38.9-62.4) for unlikely TB. Notably, most children with unlikely TB had one NIH TB criterion (81%, 61/75); specificity increased to 78.6% (95%CI 49.2-95.3) among children with unlikely TB with no NIH TB criteria. Median Mtb cfDNA concentration was higher in children with confirmed and unconfirmed TB compared to children with unlikely TB with no NIH TB criteria. Among 51 children with longitudinal samples, median Mtb cfDNA concentration decreased from 4.7 to $1.7\times10^6$ a.u. ($p<0.0001$) at median of 5.6 months (IQR 3.2-5.8) post TB treatment initiation. There was a trend for higher mortality among children with detectable Mtb-cfDNA at baseline (aHR 2.3 [95%CI 0.8-6.1], p=0.09 [adjusted for age and CD4%]).

**Conclusion:** CRISPR-TB detected Mtb cfDNA has potential to diagnose TB and monitor treatment response in CHIV, including those at greatest risk of death, using minimal blood volumes. Further evaluation in prospective pediatric cohorts is needed with appropriate negative controls.

**CRISPR-TBDB *Mtb*-cfDNA for TB diagnosis and treatment response in children with HIV at high risk for TB**

***Mtb*-cfDNA detection for TB diagnostic performance, n=153**

| | Confirmed TB | Unconfirmed TB (N=65) | | Unlikely TB (N=75) | |
|---|---|---|---|---|---|
| | Microbiologic confirmation N=13 | Clinical TB diagnosis N=46 | No clinical TB diagnosis N=19 | Any NIH TB Criterion N=61 | No NIH TB Criteria N=14 |
| ***Mtb* cfDNA+ children #** | 13 | 39 | 13 | 34 | 3 |
| **Sensitivity – % (95% CI)** | 100 (75.3-100) | 84.8 (71.1-93.7) | 68.4 (43.4-87.4) | -- | -- |
| **Specificity – % (95% CI)** | -- | -- | -- | 44.3 (31.5-57.6) | 78.6 (49.2-95.3) |
| **Deaths - TB untreated** | 100%; 2/2 | -- | 42.1%; 8/19 | 16.7%; 10/60 | 0%; 0/14 |
| **Deaths - TB treated** | 36.4%; 4/11 | 8.7%; 4/46 | -- | 0%; 0/1 | -- |
| ***Mtb* cfDNA Levels (×10⁶ a.u.) [a] –Median (IQR)** | 5.8 (3.2, 9.0) | 4.3 (2.0, 7.3) | 3.0 (1.1, 6.5) | 2.0 (1.1, 5.4) | 1.1 (0.99, 1.2) |
| **p-value [b]** | <0.001 | 0.002 | 0.05 | 0.06 | Reference group |

**Median *Mtb*-cfDNA levels at earliest available visit and post TBTx initiation, n=51**

| | Pre TBTx *Mtb* cfDNA Levels (×10⁶ a.u.) – Median (IQR) | Post TBTx initiation *Mtb* cfDNA Levels (×10⁶ a.u.) – Median (IQR) | p-value [c] |
|---|---|---|---|
| **All (N=51)** | 4.7 (2.6-8.4) | 1.7 (1.2-4.1) | <0.001 |
| **Confirmed TB (N=9)** | 7.0 (5.8-9.6) | 2.8 (1.4-5.1) | 0.008 |
| **Unconfirmed TB (N=41)** | 4.3 (2.5-7.9) | 1.5 (1.1-3.0) | <0.001 |
| **Unlikely TB (N=1)** | 9.2 | 3.8 | n/a |

[a] The *Mtb*-cfDNA level as detected by CRISPR-TB, positive cutoff threshold is $1.4\times10^6$ a.u.
[b] Wilcoxon rank sum test compared to Unlikely TB with No NIH Criteria.
[c] Wilcoxon matched-pairs signed-rank test.

## 646 MYCOBACTERIA-SPECIFIC CD4 T CELLS IN CHILDREN LIVING WITH HIV BEFORE AND AFTER ART

**Cheryl Day**[1], Wendy E. Whatney[1], Lisa Marie Cranmer[1], Irene Njuguna[2], Sylvia LaCourse[3], Jaclyn Escudero[3], Cecilia S. Lindestam Arlehamn[4], Loren Sasser[1], Cyrus Mugo[2], Hellen Moraa[5], Elizabeth Maleche-Obimbo[5], Dalton C. Wamalwa[5], Grace John-Stewart[3]

*[1]Emory University, Atlanta, GA, USA, [2]Kenyatta National Hospital, Nairobi, Kenya, [3]University of Washington, Seattle, WA, USA, [4]La Jolla Institute for Allergy and Immunology, La Jolla, CA, USA, [5]University of Nairobi, Nairobi, Kenya*

**Background:** Young children and those living with HIV are more likely to rapidly progress from Mycobacterium tuberculosis infection to tuberculosis (TB) disease. The capacity of ART to mediate restoration of functional mycobacteria-specific CD4 responses in children living with HIV (CLHIV) has not been well defined. We hypothesized that provision of ART in CLHIV would result in rapid increase in frequencies of mycobacteria-specific CD4 T cells.

**Methods:** Cryopreserved PBMCs were obtained from hospitalized CLHIV enrolled in the PUSH study in Nairobi, Kenya, before and 6 months after initiation of ART (n=43). PBMCs were thawed and incubated overnight in media alone or with a peptide pool of 300 T cell epitopes from BCG and TB antigens (MTB300) or staphylococcal enterotoxin B (SEB; positive control). Multiparameter flow cytometry was utilized to measure CD4 T cell expression of IFN-γ, IL-2, TNF-α, IL-17, MIP-1β, and CD40L.

**Results:** The median age of participants was 1.5 years (IQR 0.6-3.8). Median pre-ART plasma HIV viral load decreased from 5.8 $\log_{10}$ copies/ml to 2.3 $\log_{10}$ copies/ml and median CD4% increased from 13% to 20% after 6 months of ART ($p<0.001$ for both) (Table 1). Most (79%) participants were severely immunosuppressed at enrollment. CD4 T cell IL-2 and TNF-α production capacity and CD40L expression increased substantially and significantly after 6 months of ART, as determined by non-specific stimulation with SEB. However, the total frequency of MTB300-specific CD4 T cells expressing either IFN-γ, IL-2, TNF-α, IL-17, MIP-1β, or CD40L did not change significantly after 6 months of ART. Analysis of polyfunctional MTB300-specific CD4 T cell populations revealed two distinct subsets that increased after 6 months of ART: cells that co-express IFN-γ, TNF-α, and CD40L, and cells that co-express TNF-α and MIP-1β ($p<0.05$ for both).

**Conclusion:** Although absolute CD4 T cell counts, percentages, and some Th1 cytokine production capacity increased after ART, residual deficits in mycobacteria-specific CD4 T cell immunity persisted at 6 months following ART initiation among severely immunosuppressed CLHIV. These findings may explain mechanisms for persistent risk of TB during the first year of ART; moreover, they provide rationale for longer-term evaluation of IFN-γ-independent CD4 responses in CLHIV.

Table 1

| Participant Characteristics & CD4 Responses | Pre-ART Median (IQR) | 6 months post-ART Median (IQR) | p value |
|---|---|---|---|
| HIV RNA ($\log_{10}$ copies/ml) | 5.8 (5.1-6.3) | 2.3 (1.5-3.7) | <0.0001 |
| CD4 count (cells/µl) | 678 (337-1,503) | 1,345 (741-2,163) | <0.0001 |
| CD4% | 13 (9-18) | 20 (12-24) | 0.0002 |
| Severely Immunosuppressed (All ages) | 79% | 48% | 0.0034 |
| <12 months, CD4% <25% | 93% | 78% | 0.5331 |
| 12-35 months, CD4% <20% | 73% | 35% | 0.0409 |
| ≥36 months, CD4% <15% | 69% | 46% | 0.4283 |
| CD4 responses to SEB* | | | |
| %CD4+IFNγ+ | 0.77 (0.43-1.79) | 1.46 (0.96-2.26) | 0.1188 |
| %CD4+IL2+ | 0.58 (0.39-1.12) | 1.04 (0.60-1.80) | <0.0001 |
| %CD4+TNFα+ | 2.03 (1.30-4.03) | 2.62 (1.87-4.17) | 0.0501 |
| %CD4+IL17+ | 0.10 (0.05-0.19) | 0.10 (0.07-0.18) | 0.8141 |
| %CD4+MIP1β+ | 0.71 (0.33-1.54) | 0.75 (0.37-2.28) | 0.3921 |
| %CD4+CD40L+ | 11.05 (7.03-14.3) | 15.69 (9.6-19.36) | <0.0001 |
| CD4 responses to MTB300* | | | |
| %CD4+IFNγ+ | 0.011 (0.001-0.033) | 0.020 (0.007-0.029) | 0.3949 |
| %CD4+IL2+ | 0.017 (0.000-0.052) | 0.014 (0.000-0.031) | 0.7277 |
| %CD4+TNFα+ | 0.024 (0.008-0.047) | 0.032 (0.020-0.059) | 0.0803 |
| %CD4+IL17+ | 0.006 (0.000-0.028) | 0.009 (0.000-0.038) | 0.5632 |
| %CD4+MIP1β+ | 0.036 (0.000-0.095) | 0.018 (0.000-0.020) | 0.0610 |
| %CD4+CD40L+ | 0.000 (0.000-0.105) | 0.020 (0.000-0.193) | 0.7090 |
| %CD4+IFNγ+IL2-TNFα+IL17-MIP1β-CD40L+ | 0.000 (0.000-0.002) | 0.001 (0.000-0.005) | 0.0379 |
| %CD4+IFNγ-IL2-TNFα+IL17-MIP1β+CD40L- | 0.000 (0.000-0.000) | 0.001 (0.000-0.003) | 0.0034 |

*Values are shown after subtraction of background cytokine/CD40L expression in the unstimulated negative control condition.

## 647 POTENTIAL USE OF URINE LF-LAM IN DIAGNOSING ACTIVE TB IN THAI HIV-POSITIVE ADULTS

**Chawisar Janekrongtham**[1], Rangsima Lolekha[2], Anchalee Avihingsanon[3], Niorn Ariyothai[1], Rom Luengwattanapong[2], Patsaya Mookleemas[1], Chonticha Kittinunvorakoon[2], Chuenkamol Sethaputra[2], Supannee Jirajariyavej[4], Sasiwimol Ubolyam[3], Chris Fujitnirun[5], Sureerat Watcharasuwanseree[6], Thitisant P. Na Ayuthaya[7], Sanny Northbrook[2], Cheewanan Lertpiriyasuwat[1]

*[1]Division of AIDS and STIs, Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand, [2]Division of Global HIV and TB, U.S. Centers for Disease Control and Prevention, Nonthaburi, Thailand, [3]The HIV Netherlands Australia Thailand Research Collaboration, Thai Red Cross AIDS Research Center, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [4]Taksin Hospital, Department of Medicine, Bangkok Metropolitan Administration, Bangkok, Thailand, [5]Bhumibol Adulyadej Hospital, Directorate of Medical Services, Royal Thai Air Force, Bangkok, Thailand, [6]Department of Medicine, Udonthani Hospital, Udonthani, Thailand, [7]Public Health Center 28, Department of Health, Bangkok Metropolitan Administration, Bangkok, Thailand*

**Background:** Thailand has one of the highest TB/HIV burdens globally. The 2020 Thai national HIV treatment guidelines recommend rapid TB urine LF-LAM testing as an additional TB diagnostic test to assist with TB diagnosis among people living with HIV (PLHIV) who present with 1) signs and symptoms of active TB, 2) critical illness (respiration rate >30 breaths/minute, body temperature >39°C, heart rate >120 beats/minute), or 3) CD4 cell count <200 cells/mm$_3$ for in-patient and <100 cell/mm$_3$ for out-patient with or without signs and symptoms of active TB. This study assesses the yield of the Alere Determine™ TB LF-LAM test in diagnosing active TB in PLHIV and factors associated with positivity.

**Methods:** National TB/HIV data from PLHIV at least 15 years old who met eligibility criteria for urine LF-LAM testing at 17 hospitals in 8 provinces from October 2020 to August 2021 were analyzed. Definite TB diagnosis is defined as having single sputum Xpert-MTB/RIF and TB culture positivity or either of these two diagnoses independently. Probable TB is defined as a clinical diagnosis by a doctor, abnormal chest X-ray, and being treated with TB regimens. We examined urine LF-LAM test accuracy, sensitivity, and specificity in diagnosing definite and probable TB and performed random effects logistic regression modeling to identify factors associated with urine LF-LAM positivity.

**Results:** Of 488 PLHIV with urine LF-LAM test results, 179 (37%) were TB cases including 45 (25%) definite TB and 134 (75%) probable TB. The median age was 39 years, 118 (65%) were in-patients, and 131 (73%) were male. Table 1 shows test performance in assisting in the diagnosis of definite and probable TB cases. Overall LF-LAM test accuracy, sensitivity and specificity were 79%, 60%, and 90%, respectively and higher among CD4 <200 cells/mm$_3$ at 81%, 66%, and 92%, respectively. The Positive Predictive Value was 83% among CD4 <200 cells/mm$_3$ and 41% among CD4 >200 cells/mm$_3$. Multivariable logistic regression revealed LF-LAM positivity among PLHIV with TB disease associated with CD4 <100 cells/mm$_3$ (aOR: 3.47, 95% CI 1.22 – 9.86) and clinical weight loss (aOR: 3.57, 95% CI 1.83 – 6.96) after adjusting for hospital type.

**Conclusion:** The LF-LAM urine testing can assist in diagnosing active TB in PLHIV with CD4 <200 cells/mm$_3$ in Thailand. Specificity was high, but the LF-LAM should be used in combination with other TB diagnostics for the most accurate diagnosis. The benefits of using LF-LAM in improving patient outcomes should be further studied.

| Categories/Statistics | | Sensitivity (95% CI) n/N | Specificity (95% CI) n/N | Positive Predictive Value (95% CI) n/N | Negative Predictive Value (95% CI) n/N | Accuracy (95% CI) n/N | True prevalence n/N | Apparent prevalence n/N |
|---|---|---|---|---|---|---|---|---|
| TB disease | All CD4 (n=488) | 60% (52.20, 67.02) 107/179 | 90% (86.43, 93.35) 279/309 | 78% (71.60, 83.84) 107/137 | 79% (76.11, 82.10) 279/351 | 79% (75.11, 82.53) 386/488 | 37% 179/488 | 28% 137/488 |
| | CD4 <200 (n=402) | 63% (54.88, 70.41) 100/159 | 92% (87.57, 94.90) 223/243 | 83% (76.37, 88.55) 100/120 | 79% (75.47, 82.28) 223/282 | 80% (76.12, 84.12) 323/402 | 40% 159/402 | 30% 120/402 |
| | CD4 ≥200 (n=86) | 35% (15.39, 59.22) 7/20 | 85% (73.90, 92.49) 56/66 | 41% (23.46, 61.53) 7/17 | 81% (75.45, 85.78) 56/69 | 73% (62.62, 82.23) 63/86 | 23% 20/86 | 20% 17/86 |
| Definite TB | All CD4 (n=354) | 60% (44.33, 74.30) 27/45 | 90% (86.43, 93.35) 279/309 | 47% (37.87, 58.32) 27/57 | 94% (91.34, 95.58) 279/297 | 86% (82.33, 89.75) 306/354 | 13% 45/354 | 16% 57/354 |
| | CD4 <200 (n=281) | 66% (45.99, 78.19) 24/38 | 92% (87.57, 94.90) 223/243 | 55% (43.47, 66.99) 24/44 | 94% (90.97, 95.87) 223/237 | 88% (83.35, 91.36) 247/281 | 14% 38/281 | 16% 44/281 |
| | CD4 ≥200 (n=73) | 43% (9.90, 81.59) 3/7 | 85% (73.90, 92.49) 56/66 | 23% (10.10, 46.78) 3/13 | 93% (87.47, 96.24) 56/60 | 81% (69.73, 88.96) 59/73 | 10% 7/73 | 18% 13/73 |
| Probable TB | All CD4 (n=443) | 60% (50.89, 68.08) 80/134 | 90% (86.43, 93.35) 279/309 | 73% (64.60, 79.19) 80/110 | 84% (80.92, 86.57) 279/333 | 81% (77.15, 84.65) 359/443 | 30% 134/443 | 25% 110/443 |
| | CD4 <200 (n=364) | 63% (53.56, 71.42) 76/121 | 92% (87.57, 94.90) 223/243 | 79% (70.73, 85.39) 76/96 | 83% (79.85, 86.37) 223/268 | 82% (77.89, 86.00) 299/364 | 33% 121/364 | 26% 96/364 |
| | CD4 ≥200 (n=79) | 31% (9.09, 61.43) 4/13 | 85% (73.90, 92.49) 56/66 | 29% (12.51, 51.14) 4/14 | 86% (81.54, 90.36) 56/65 | 76% (65.29, 85.06) 60/79 | 16% 13/79 | 18% 14/79 |
| TB disease regardless of signs and symptoms of active TB and critical illness | In-patients with CD4 <200 (n=25) | 62% (31.58, 86.14) 8/13 | 83% (51.59, 97.91) 10/12 | 80% (51.25, 93.83) 8/10 | 67% (49.01, 80.63) 10/15 | 72% (50.61, 87.93) 18/25 | 52% 13/25 | 40% 10/25 |
| | Out-patients with CD4 <100 (n=61) | 67% (22.28, 95.67) 4/6 | 96% (87.47, 99.56) 53/55 | 67% (31.43, 89.73) 4/6 | 96% (89.51, 98.80) 53/55 | 93% (84.05, 98.18) 57/61 | 10% 6/61 | 10% 6/61 |

## 648 HIGHLY PERFORMANT MULTIPLEX PCR FOR TB AND NTM INFECTIONS IN PERSONS WITH HIV

**Yeya dit Sadio Sarro**[1], Bassirou Diarra[2], Bocar Baya[1], Ousmane Kodio[1], Fanta Sanogo[1], Djakaridja Daniogo[1], Ibrahim B. Diallo[1], Mohamed Tolofoudie[1], Chad J. Achenbach[3], Seydou Doumbia[1], Babafemi O. Taiwo[3], Robert Murphy[3], Sally M. McFall[3], Mamoudou Maiga[3]

*[1]University of Sciences, Techniques and Technologies of Bamako (USTTB), Bamako, Mali, Bamako, Mali, [2]University of Sciences, Techniques and Technologies of Bamako (USTTB), Bamako, Mali, [3]Northwestern University, Chicago, IL, USA*

**Background:** The prevalence of non-tuberculous mycobacteria (NTM) infection has been increasing in countries throughout the world regardless of income level. HIV infected patient are at risk to be infected by tuberculosis and NTM due to their immunocompromised situation. NTM infection is clinically indistinguishable from tuberculosis posing significant challenges in patient management, especially in patients chronically treated for pulmonary TB. In this study, we evaluated a new highly sensitive Multiplex MTB/NTM assay that can differentiate M. tuberculosis complex (MTBC) from all NTM, including the treatable and most common NTM, M. avium complex (MAC) in persons with and without HIV. We hypnotized that this new RT-PCR assay will be as sensible as sputum culture and have a shorter turn around time.

**Methods:** We developed and optimized a new open- Multiplex MTB/NTM assay which detects specifically TB and MAC and all other Mycobacterium species. Samples were spiked with stored isolates and testing 20 replicates. Patients with presumptive TB and NTM were enrolled at the Respiratory Disease Department of The University Teaching Hospital of Point G, in Mali for the clinical evaluation. All the enrolled patients were tested for HIV and Tuberculosis molecular test recommended by WHO (Xpert MTB/RIF®). The diagnostic performance of the new assay was calculated using sputum culture as reference and Gen-Probe Accuprobe® for MAC identification.

**Results:** In the development stage, the new assay displayed high analytic performance with 100% detection of MTBC and MAC at 5 colony forming units (CFUs) per milliliter of sputum. Overall, excluding the tuberculosis treatment failure cases, the Multiplex assay showed sensitivity, specificity, PPV and NPV of 83.3% [66.4-92.6], 96.6% [88.6-99.0], 92.5% [82.3-96.5] and 92.2% [82.7-96.5], and the comparator assay (Xpert MTB/RIF) had values of 96·7% [83.3-99.4], 80.0% [68.2-88.1], 70·7 [55.5-82.3] and 97.9% [89.3-99.6], respectively. For the HIV infected group, the Xpert MTB/RIF assay showed higher sensitivity (96.4% vs. 71.4%, respectively), but the Multiplex was more specific (96.2% vs. 76.9%) (See Table). The Multiplex assay successfully detected all (5/5) MAC cases.

**Conclusion:** Our new Multiplex assay demonstrates better specificity than Xpert for all groups studied, in addition to detecting potential NTM cases. The assay could therefore complement the widely used Xpert assay and enhance discrimination of MTBC and NTM infections.

**Abstract Table:** Multiplex and Xpert MTB/RIF diagnostic performances relative to sputum culture

| | | Multiplex RT-PCR | Xpert MTB-RIF |
|---|---|---|---|
| All participants (N=190) | Sensitivity (%) [CI] | 80·4 [66·8-89·3] | 93·4 [82·85-97·7] |
| | Specificity (%) [CI] | 85·7 [77·7-91·1] | 61·9 [52·3-70·6] |
| | PPV (%) [CI] | 71·1 [57·7-81·6] | 51·8 [41·2-62·2] |
| | NPV (%) [CI] | 90·9 [83·6-95·1] | 95·5 [87·8-98·4] |
| TB Patient Naïve to treatment (N=30) | Sensitivity (%) [CI] | 82·4 [58·9–93·8] | 94·1 [73·0–98·9] |
| | Specificity (%) [CI] | 90·9 [62·2–98·3] | 81·8 [52·3–94·8] |
| | PPV (%) [CI] | 93·3 [70·1–98·8] | 88·9 [67·2–96·9] |
| | NPV (%) [CI] | 76·9 [49·7–91·8] | 90.0 [59.5–98·2] |
| HIV Patient (N=36) | Sensitivity (%) [CI] | 71·4 [52·9–84·7] | 96·4 [82·2–99·3] |
| | Specificity (%) [CI] | 96·2 [81·1–99·3] | 76·9 [57·9–88·9] |
| | PPV (%) [CI] | 95·2 [77·3–99·1] | 81·8 [65·6–91·3] |
| | NPV (%) [CI] | 75·8 [58·9 – 87·1] | 95·2 [77·3 -99·1] |

*CI: confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value*

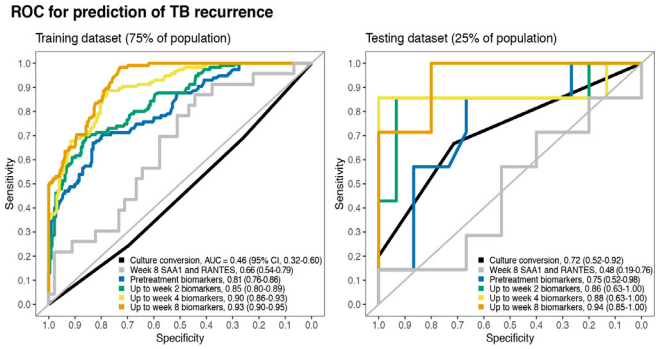
## 649 BLOOD-BASED PATHOGEN AND HOST BIOMARKER SIGNATURES THAT PREDICT TB TREATMENT OUTCOMES

**Marjorie Z. Imperial**[1], George Sigal[2], Anu Mathew[2], Leah Jarlsberg[1], Patrick P. Phillips[1], Jon Jacobs[3], Mingyue Wang[2], Tatiana Plisova[2], Christopher Campbell[2], J Lucian Davis[4], William Whitworth[5], Jeff Schorey[6], David Lewinsohn[7], Rada Savic[1], Payam Nahid[1]

*[1]University of California San Francisco, San Francisco, CA, USA, [2]Meso Scale Diagnostics, LLC, Rockville, MD, USA, [3]Pacific Northwest National Laboratory, Richland, WA, USA, [4]Yale University, New Haven, CT, USA, [5]Centers for Disease Control and Prevention, Atlanta, GA, USA, [6]University of Notre Dame, Notre Dame, IN, USA, [7]Oregon Health and Sciences University, Portland, OR, USA*

**Background:** We integrated blood-based pathogen antigenic detection and host proteomic biomarkers to predict culture conversion status and TB recurrence.

**Methods:** A total of 628 clinical trial and cohort participants were included in the analysis: 538 from two Phase IIB trials (TBTC Study 29/29X) that collected serum at 2 time points (pretreatment and week 8) and 90 (60 cured, 30 recurrences) from a Phase III trial (REMoxTB) and cohort studies, provided by the Markedly Accelerating Research with Knowledge of TB Biomarkers Biobank, that collected serum at 7 time points (pretreatment and weeks 2, 4, 8, 17, 26, and 52). Levels for 54 host proteins and one pathogen antigenic detection marker (lipoarabinomannan, LAM) were available for analysis. Nonlinear mixed effect modeling and machine learning algorithms were used to search for biomarker signatures that predict culture conversion status at 8 weeks (all participants), time to positivity in the MGIT assay during treatment (N=538), and TB recurrence up to 18 months after start of treatment (N=90). A random 75% of the population was used for training and 25% for testing. Area under the receiver operating characteristic curve (ROC AUC) was used to assess model discrimination.
**Results:** With a ROC AUC of 0.77 (95% CI, 0.68-0.85), week 8 serum amyloid A1 (SAA1) and regulated on activation, normal T cell expressed and secreted (RANTES) levels were found to predict longitudinal time to positivity and culture conversion status at 8 weeks. Week 8 SAA1 and RANTES poorly predicted TB recurrence with a ROC AUC < 0.50. A reanalysis of all biomarkers for prediction of TB recurrence resulted in biomarker signatures with ROC AUC of 0.75 (0.52-0.98) using pretreatment levels, 0.86 (0.63-1.00) using pretreatment to week 2 levels, 0.88 (0.63-1.00) using pretreatment to week 4 levels, and 0.94 (0.85-1.00) using pretreatment to week 8 levels (Figure). Host neopterin, tumor necrosis factor-beta (TNF-β) and triggering receptor expressed on myeloid cells 1 (TREM1) levels and pathogenic LAM levels in blood were the top biomarkers that predict TB recurrence, suggesting that biomarkers for clinical outcomes may be different from biomarkers for culture conversion.
**Conclusion:** Integrated host and pathogen blood-based signatures have potential to provide an alternative, non-culture based tool to project long term relapse-free outcomes and to help inform both clinical care and the design of TB clinical trials.




## 650 IMPAIRED DLCO CORRELATES WITH REDUCED TOTAL LUNG GLYCOLYSIS AFTER TB TREATMENT

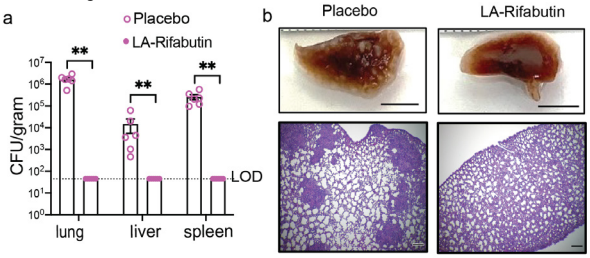
**Patrick De Marie C. Katoto**[1], Sandra Mukasa[1], Karen Wolmarans[1], Antoneta Mashinyira[1], Reto Guler[1], Friedrich Thienemann[1]
[1]*University of Cape Town, Cape Town, South Africa*

**Background:** Mortality rates after successful completion of tuberculosis (TB) treatment remain elevated and healthy survival is impaired by chronic lung disease. In our ongoing StatinTB trial (ClinicalTrials.gov Identifier: NCT04147286), we aim to reduce persistent lung inflammation with statins in a proof-of-concept phase IIB, double-blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of 40 mg atorvastatin to reduce persistent lung inflammation after successful TB treatment completion in HIV-infected and HIV-uninfected adults measured by PET/CT. We report the association between diffuse lung capacity and persistent lung inflammation of the first included participants.
**Methods:** Participants with clinical response to TB treatment and a negative sputum Mtb culture at 16 weeks were screened at the end of a 24-week course of treatment for drug-sensitive TB. Lung function and persistent lung inflammation were measured using EasyOne Pro® Lab and 18F-FDG-PET/CT respectively. Total lung glycolysis (TLG) was calculated to estimate level of lung inflammation. Persistent inflammation was defined as TLG ≥50 SUVbw*mL.
**Results:** Of the 45 participants (30 males) aged 35.4 ±12.6 years who underwent PET/CT, 8 (17.8%) were HIV positive, 26 (57.8%) were smokers and 9 (20%) had previous history of TB. Persistent inflammation was detected among 16 (35.6%) participants with a mean of TLG 245 ±194 SUVbw*mL. Fibro-cystic disease such as bronchiectasis, important distortion of lung architecture (large bullae and fibrotic bands) and a reduced DLCO were common among participants with persistent inflammation. In addition, FEV1, FVC and DLCO were reduced in participants with HIV/TB co-infection compared to participants with TB alone. After adjusting for other variables in the models, DLCO was inversely associated with TLG with (OR, 95%CI: 0.26, 0.08-0.90, p=0.031) or without (OR, 95%CI: 0.22, 0.06-0.82, p=0.024) HIV status being held constant in the model.
**Conclusion:** Impaired DLCO is associated with persistent lung inflammation among young adults with excellent adherence to a 24-weeks treatment regimen for drug-sensitive TB. Therapeutic strategy to reduce persistent lung inflammation in Post TB treatment requires further evaluation as it is likely to improve pulmonary function.

## 651 RIFABUTIN FORMULATION THAT DELIVERS DRUG 4 MONTHS PREVENTS AND TREATS Mtb INFECTION

**Manse Kim**[1], Claire E. Johnson[1], Alan A. Schmalstig[1], Ayano Annis[1], Sarah E. Wessel[1], Miriam Braunstein[1], J. Victor Garcia-Martinez[1], Martina Kovarova[1]
[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** Tuberculosis (TB) is a major cause of morbidity and mortality worldwide for people living with HIV. Rifabutin (RFB) is an anti-TB drug with potent anti-bactericidal activity, low minimum inhibitory concentration (MIC, 64 ng/ml), long terminal half-life, higher tissue uptake and reduced potential for drug-drug interactions compared to other TB drugs from the rifamycin family. Successful TB treatment requires strict adherence to drug regimens for prolonged periods of time. Long-acting (LA) injectable drug formulations can potentially simplify TB treatment by reducing drug dosing intervals, improving adherence to treatment regimens. We developed LA injectable RFB formulations (LA-RFB) made of biodegradable polymers, that solidify after subcutaneous injection that can efficiently deliver drug for 4 months.
**Methods:** Twenty-one LA-RFB formulations with various composition were first evaluated for release properties in vitro. Then, RFB plasma concentration was assessed for 4 months in BALB/c mice (n=4) administered a single subcutaneous injection of optimized LA-RFB (15 mg RFB/dose). RFB tissue penetration (lung, liver, spleen, kidney, and lymph nodes) was analyzed at 2-and 6-weeks post administration. The efficacy of the LA-RFB formulation was evaluated in BALB/c mice (n=6) after pre- or post-exposure to Mtb via aerosol (~200 CFU). Bacterial burden was quantitated in lung, liver, and spleen (CFU/g of tissue) and lung pathology was evaluated by immunohistochemistry.
**Results:** The selected LA-RFB formulation provided RFB plasma concentrations above the MIC for 16 weeks post administration. Mean tissue RFB concentrations six-weeks post injection were: 6.7 ± 1.6 µg/g lung, 7.8 ± 2.1 µg/g liver, 9.0 ± 2.1 µg/g spleen, 8.3 ± 1.7 µg/g kidney, 14.0 ± 3.2 µg/g lymph nodes (mean ± S.E.M.). A high tissue to plasma ratio of drug was observed in lung 15.4 (median, range 12.4-23.7). BALB/c mice treated with LA-RFB pre- Mtb exposure were fully protected from the infection. Post exposure treatment resulted in clearance of existing Mtb infection in lung, prevention of Mtb dissemination to distal organs (Figure 1a) and no lung pathology (Figure 1b).
**Conclusion:** The LA-RFB formulation can deliver drug for four months after a single subcutaneous injection, efficiently prevents Mtb infection, treats existing Mtb infection, and prevent Mtb dissemination to distal organs. LA-RFB provides a proof of concept for the further development of multiple LA formulations of anti-TB drugs.




## 652 ISONIAZID AND RIFAMPIN PLASMA EXPOSURE ARE ASSOCIATED WITH TB TREATMENT OUTCOMES

**Lauren S. Peetluk**[1], Edward Acosta[2], David W. Haas[1], Brian Hachey[1], Gustavo Amorim[1], Marcelo Cordeiro-Santos[3], Afrânio L. Kritski[4], Marina C. Figueiredo[1],

Leticia Linhares[1], Megan Turner[1], Felipe Ridolfi[5], Bruno B. Andrade[6], Valeria Cavalcanti Rolla[5], Timothy Sterling[1]
*[1]Vanderbilt University, Nashville, TN, USA, [2]University of Alabama at Birmingham, Birmingham, AL, USA, [3]Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, Manaus, Brazil, [4]Clínica de Família Rinaldo Delamare, Rio de Janeiro, Brazil, [5]Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, [6]Instituto Brasileiro para Investigação da Tuberculose, Salvador, Brazil*

**Background:** Previous studies suggest that individual drug pharmacokinetics affect tuberculosis (TB) treatment effectiveness and safety, but findings have been inconsistent. It is unclear if and when (during treatment) therapeutic drug monitoring could improve TB treatment outcomes. We evaluated TB drug exposure and treatment outcome associations in a large prospective cohort of TB cases in Brazil.
**Methods:** Participants were from the Regional Prospective Observational Research for Tuberculosis (RePORT)-Brazil cohort study. Analyses included culture-confirmed pulmonary TB cases who started a standard TB treatment regimen (2 months of isoniazid (H), rifampin (R), pyrazinamide (Z) and ethambutol (E), then 4 months of HR) between 2015 and 2019, and had ≥ 1 blood sample within 7 hours of a drug dose; follow-up was for 24 months from enrollment. Plasma H, R, Z, E and desacetyl-rifampin (d-R) were quantified by multiplex mass spectrometry at baseline, month 1, month 2, and end of treatment. Individual drug exposure was categorized based on population distributions as high (>75th percentile), middle (25th-75th percentile), and low (<25th percentile), and below levels of quantification (BLQ). Effectiveness outcomes were TB treatment failure and recurrence; safety outcomes were Grade 3 or higher (3+) adverse events (AE) and Grade 2 or higher hepatotoxicity.
**Results:** There were 933 plasma samples assayed from 485 cases; 117 (24%) were people with HIV (PWH). Overall, 16 (3%) had treatment failure/recurrence, 19 (4%) had Grade 3+ AE, and 23 (5%) had hepatotoxicity. Each outcome was more common in PWH: 6% vs. 2% treatment failure/recurrence, 9% vs. 2% Grade 3+ AE, 8% vs. 4% hepatotoxicity. R exposure, but not H, Z, or E, was lower in PWH. Low month 1 exposure to H and d-R was associated with failure/recurrence (Table). After adjusting for HIV status, high exposure to H, R and d-R were associated with Grade 3+ AE, and high exposure to d-R was associated with hepatotoxicity (Table). Exposure categories for Z and E were not significantly associated with effectiveness or toxicity.
**Conclusion:** TB treatment was generally effective and safe in this study population, though less so among PWH. Associations of low month 1 H and d-R concentrations with failure/recurrence, and high H, R and d-R exposure with toxicity suggest a potential role for therapeutic drug monitoring to improve TB treatment effectiveness and safety.

| | Treatment failure/recurrence (TF/R) based on drug levels at Month 1 | | | Longitudinal analysis of toxicity outcomes[2] | |
|---|---|---|---|---|---|
| **Plasma drug exposure** | No TF/R N = 338 | TF/R N = 8 | **p-value**[1] | Grade 3+ AE OR (95% CI) | Hepatotoxicity OR (95% CI) |
| Isoniazid, n (%) | | | **0.03** | | |
| BLQ | 13 (87) | 2 (13) | | 2.6 (0.3, 23.4) | [ - ] |
| Low | 84 (97) | 3 (3.4) | | [ - ] | 0.3 (0.0, 2.7) |
| Middle | 162 (98) | 3 (1.8) | | Ref. | Ref. |
| High | 79 (100) | 0 (0) | | **4.5 (1.2, 17.7)** | 2.5 (0.7, 8.5) |
| Rifampin, n (%) | | | 0.85 | | |
| BLQ | 50 (96) | 2 (3.8) | | 4.0 (0.7, 22.6) | 0.4 (0.0, 3.4) |
| Low | 81 (98) | 2 (2.4) | | [ - ] | 0.6 (0.1, 2.3) |
| Middle | 143 (98) | 3 (2.1) | | Ref. | Ref. |
| High | 64 (98) | 1 (1.5) | | **8.1 (1.6, 42.4)** | 2.2 (0.7, 7.5) |
| Desacetyl-Rifampin, n (%) | | | **0.05** | | |
| BLQ | 65 (96) | 3 (4.4) | | 3.3 (0.6, 18.4) | 1.1 (0.1, 11.3) |
| Low | 77 (95) | 4 (4.9) | | [ - ] | 1.0 (0.1, 10.4) |
| Middle | 139 (99) | 1 (0.7) | | Ref. | Ref. |
| High | 57 (100) | 0 (0) | | **6.7 (1.4, 32.1)** | **13.2 (2.7, 65.0)** |
| Ethambutol, n (%) | | | 0.27 | | |
| BLQ | 5 (100) | 0 (0) | | 1.03 (0.1, 9.0) | [ - ] |
| Low | 45 (94) | 3 (6.2) | | 0.5 (0.1, 4.7) | 0.3 (0.0, 2.1) |
| Middle | 189 (98) | 4 (2.1) | | Ref. | Ref. |
| High | 99 (99) | 1 (1.0) | | 2.4 (0.6, 9.1) | 1.4 (0.5, 4) |
| Pyrazinamide, n (%) | | | 0.84 | | |
| BLQ | 10 (100) | 0 (0) | | 0.6 (0.1, 5.1) | [ - ] |
| Low | 74 (97) | 2 (2.6) | | 1.1 (0.2, 5.9) | 0.4 (0.0, 3.1) |
| Middle | 175 (97) | 5 (2.8) | | Ref. | Ref. |
| High | 79 (99) | 1 (1.2) | | 1.6 (0.4, 7.2) | 2.5 (0.7, 8.6) |

AE=adverse event; BLQ = below level of quantification; low=drug exposure <25th percentile; middle = drug exposure in 25th – 75th percentile; high = drug exposure >75th percentile
[1]Fisher's exact test
[2]Logistic regression analysis with robust standard errors, adjusted for HIV
[ - ] could not be estimated because of 0 cells
**Bold** indicates statistical significance (p<0.05)

## 653 ALCOHOL USE AND SUBOPTIMAL ADHERENCE TO ISONIAZID IN PERSONS WITH HIV AND LATENT TB

**Winnie R. Muyindike**[1], Robin Fatch[2], Debbie M. Cheng[3], Nneka I. Emenyonu[2], Leah Forman[3], Christine Ngabirano[4], Julian Adong[4], Benjamin Linas[3], Karen R. Jacobson[3], Judith A. Hahn[2]
*[1]Mbarara Regional Referral Hospital, Mbarara University of Science and Technology, Mbarara, Uganda, [2]University of California San Francisco, San Francisco, CA, USA, [3]Boston University, Boston, MA, USA, [4]Mbarara University of Science and Technology, Mbarara, Uganda*

**Background:** Isoniazid preventive therapy (IPT) is a key strategy to decrease tuberculosis (TB) disease development in people living with HIV (PLHIV). Unhealthy alcohol use is associated with increased risk of progression to TB disease and reduced adherence to antiretroviral therapy (ART), but its effect on IPT adherence is not well known. We sought to determine the level of adherence to IPT, overall and by drinking status among PLHIV in Uganda.
**Methods:** This was a prospective study of PLHIV with confirmed latent TB infection (LTBI), all on ART, in a large HIV clinic in Southwestern Uganda. We recruited 200 PLHIV reporting any current (prior 3 months) alcohol use and 102 PLHIV reporting no alcohol consumption for at least 1 year. All received IPT. We monitored adherence with Medication Event Monitoring System (MEMS) caps. Our primary outcome, sub-optimal INH adherence, was defined as <90% of days with any MEMS opening in the prior 90 days. Alcohol use was captured by a composite measure of the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) and phosphatidylethanol (PEth), an alcohol biomarker. Alcohol use was categorized as: none: no self-report, and PEth <8 ng/mL; moderate: AUDIT-C 1-2 (women) or 1-3 (men), and/or PEth 8-<50 ng/mL; unhealthy: AUDIT-C ≥3 (women) or ≥4 (men), and/or PEth ≥50 ng/mL. We used generalized estimating equations logistic regression to assess the association between the alcohol use and sub-optimal INH adherence, adjusting for age, gender, ART adherence, study time on INH, symptoms of depression, Grade 2+ liver enzyme elevations or symptoms and social support.
**Results:** Of the 302 enrolled persons, 279 were on INH for three or more months. Half (50.9%) were female and 21.9% and 50.5% were in the moderate and unhealthy alcohol groups, respectively. Overall prevalence of sub-optimal INH adherence was 31.3% at 3 months and 43.9% at 6 months. The odds of sub-optimal INH adherence were significantly higher for those in the unhealthy (adjusted odds ratio [aOR] 2.52 (95% CI: 1.48-4.30)) alcohol group but not in the moderate (aOR 1.46 (95% CI: 0.87-2.45)) group, compared to no alcohol consumption group.
**Conclusion:** Sub-optimal adherence to INH at 3- and 6-months was high among PLHIV and was associated with unhealthy alcohol use. Adherence support and/or alcohol reduction strategies are needed for this group at high risk for active TB.

**Unadjusted and Adjusted Odds Ratios (OR)* and 95% Confidence Intervals (CI) for INH adherence <90% in the prior 3 months among PWH with latent TB (n = 539 observations; n = 279 participants).**

| | Unadjusted OR (95% CI) | p-value | Adjusted OR** (95% CI) | p-value |
|---|---|---|---|---|
| Alcohol use, prior 3 months (ref = None) | 1.00 | <0.01 | 1.00 | <0.01 |
| Moderate | 1.50 (0.93, 2.42) | | 1.46 (0.87, 2.45) | |
| Unhealthy | 2.58 (1.61, 4.14) | | 2.52 (1.48, 4.30) | |
| Age (per 1 year decrease) | 1.05 (1.02, 1.07) | <0.01 | 1.05 (1.02, 1.08) | <0.01 |
| Gender (ref = Female) | 1.00 | 0.04 | 1.00 | 0.31 |
| Male | 1.54 (1.01, 2.34) | | 1.30 (0.79, 2.13) | |
| ART adherence, prior 30 days (ref = Excellent/very good) | 1.00 | <0.01 | 1.00 | <0.01 |
| Good/fair/poor/very poor | 2.17 (1.35, 3.48) | | 2.44 (1.46, 4.10) | |
| Study visit (ref = 3 months) | 1.00 | <0.01 | 1.00 | <0.01 |
| 6 months | 1.72 (1.34, 2.21) | | 1.84 (1.38, 2.45) | |

*GEE logistic regression models, exchangeable working correlation with robust empirical standard errors
**Multivariable model also adjusted for symptoms of depression, Grade 2+ liver enzyme elevations or other symptoms, and social support.

## 654 DOSE SELECTION OF RIFAPENTINE IN PEDIATRIC PATIENTS BASED ON PBPK MODELLING

New Investigator Scholar

**Maiara C. Montanha**[1], Shakir A. Atoyebi[1], Fazila S. Bunglawala[1], Kamunkhwala Gausi[2], Hannah Kinvig[1], Paolo Denti[2], Marco Siccardi[1], Catriona Waitt[1]
*[1]University of Liverpool, Liverpool, UK, [2]University of Cape Town, Cape Town, South Africa*

**Background:** Rifapentine (RPT) is an antibiotic approved for the treatment of Mycobacterium tuberculosis. Although the pharmacokinetics (PK) of RPT has been investigated in adults and children above 2 years, supporting twice-weekly dosing, no studies have assessed the PK of this drug in younger children. The study aimed to apply physiologically-based pharmacokinetic (PBPK) modelling to predict the PK of RPT in this population.
**Methods:** A whole-body PBPK model was designed in Simbiology (MATLAB R2019a) and used to simulate 100 adult and paediatric individuals. First, the model was qualified against reported clinical data for oral (PO) and intravenous (IV) Midazolam (MDZ – used as a "probe" for CYP3A4 metabolism) and RPT PO

in healthy adults. Physiological changes were incorporated into the model to provide a mathematical description of paediatric population. The paediatric model was qualified against reported clinical data for MDZ (IV and PO, 6 months – 12 years of age) and RPT (PO, >2 years of age). The model was assumed to be verified if the absolute average-fold error (AAFE) was below 2. The qualified model was then used to simulate single-doses of RPT PO 15 mg/kg and 25 mg/kg stratified into 3 age groups: 1 – 6 (group 1), 6 – 12 (group 2), and 12 – 24 (group 3) months. The estimated ratio between RPT free-plasma concentration (unbound to albumin) and the minimum inhibitory concentration (MIC) for M. tuberculosis (0.05 µg/ml) was calculated 48 and 72 hours after administration, since no PK/PD target is defined.

**Results:** The PBPK model was successfully qualified for MDZ and RPT with an AUC0-inf AAFE of 1.2 and 1.04 for adult individuals and 1.14 and 1.25 for paediatric individuals, respectively. The ratio of the estimated RPT free-plasma concentration and M. tuberculosis MIC at 48 and 72 h after administration of 15 mg/kg and 25 mg/kg were: 1.2 ± 0.4 and 1.8 ± 0.6, 0.5 ± 0.2 and 0.7 ± 0.4 (group 1); 0.8 ± 0.3 and 1 ± 0.4, 0.3 ± 0.2 and 0.4 ± 0.2 (group 2); 0.7 ± 0.4 and 1 ± 0.4, 0.2 ± 0.1 and 0.4 ± 0.2 (group 3), respectively. The dose of 25 mg/kg seems to be indicated for children younger than 2 years (table 1), although for those younger than 6 months the dose of 15 mg/kg achieves the AUC0-168 observed in adults (410 mg.h/L) for a dose of RPT PO 900 mg once weekly.

**Conclusion:** PBPK modelling provides a rational framework to predict PK in complex clinical scenarios. The reduced CL observed in group 1 is due to the maturation process of CYP3A4 enzymes involved in the RPT metabolism.

**Table 1.** Simulated pharmacokinetic parameters of rifapentine following oral administration in children younger than 2 years.

| | RPT dose 15mg/kg | | | RPT dose 25mg/kg | | |
|---|---|---|---|---|---|---|
| Parameters | Group 1 | Group 2 | Group 3 | Group 1 | Group 2 | Group 3 |
| $AUC_{0-168}$ (mg.h/L) | 358.3 (25.9) | 306.1 (26.3) | 270.7 (23.8) | 550.9 (22) | 421.3 (22.5) | 363.5 (26.5) |
| $C_{max}$ (mg/L) | 12.5 (20.7) | 12.7 (19.7) | 11.2 (19.3) | 18.9 (16.8) | 17.1 (16.1) | 14.6 (18.7) |
| CL/F (L/h) | 1.1 (5.6) | 1.2 (8.8) | 1.4 (9.5) | 1.1 (5.2) | 1.2 (8.6) | 1.4 (10) |

Data are presented as the mean (coefficient of variation, %). $AUC_{0-168}$, area under the plasma concentration-time curve over a dosing interval of one week. $C_{max}$ maximum plasma concentration. CL/F, apparent clearance.

## 655 CONCENTRATION-QT MODELING OF BEDAQUILINE, CLOFAZIMINE, AND PRETOMANID IN TB PATIENTS

**Mahmoud T. Abdelwahab**[1], Elin Svensson[2], Andreas Diacon[3], Almari Conradie[4], Morounfolu Olugbosi[4], Rodney Dawson[5], Gary Maartens[1], Paolo Denti[1]
*[1]University of Cape Town, Cape Town, South Africa, [2]Radboud Institute of Health Sciences, Radboud University Medical Center, Nijmegen, Netherlands, [3]Task Applied Science, Bellville, South Africa, [4]Global Alliance for TB Drug Development, New York, NY, USA, [5]Division of Pulmonology and Department of Medicine, University of Cape Town Lung Institute, Cape Town, South Africa*

**Background:Bedaquiline** (BDQ), clofazimine (CFZ), and pretomanid (PRET) are used for drug-resistant TB (DR-TB). BDQ, through its main metabolite M2, CFZ, and PRET have all been associated with QT interval prolongation. Due to the multidrug nature of tuberculosis treatment, there is a risk of additive cardiac toxicity. Limited information is available on the drug-drug interactions and combined toxicity of these drugs.

**Methods:** Adult drug-susceptible TB patients were enrolled in a 14-day early bactericidal activity study of CFZ, alone or in combination with BDQ or PRET. 105 patients were randomised into 7 treatment arms. BDQ was administered as 400mg on day one, 300mg on day two, and 200mg on days 3-14. CFZ was given as 300mg for 3 days, followed by 100mg until day 14. PRET was given as 200mg daily. ECGs were performed in triplicate at predose, 5, and 10 hours one day before treatment (relative to the anticipated time of dose) and matched with plasma samples on days 1-3, 8, and 14. Diurnal variation in QTcF was described using oscillator functions. The drugs' effects were described with linear and Emax models and their combined effect was tested with competitive interaction models.

**Results:** Pretreatment QTcF data from all arms and post-treatment data from arms with non-QT prolonging drugs (105 patients, 973 observations) were used to characterise baseline covariates. The data from arms containing BDQ, CFZ, and PRET (75 patients, 1089 observations) were used to characterise the concentration-QTcF relationship and investigate interactions. QTcF diurnal variation was described by three cosine functions. M2 and CFZ effects were described by Emax model with a maximum QT prolongation of 29.4 and 35.9ms and $EC_{50}$ of 0.371 and 0.854mg/L, respectively. PRET effect was described by linear model with a slope of 1.98ms·L/mg. We identified a competitive interaction between M2 and CFZ. The effect of PRET was additive to the other drugs.

**Conclusion:** We present a joint concentration-QTcF model of BDQ, CFZ, and PRET. We confirmed the QT-prolonging effect of all three. The interaction between M2 and CFZ causes a less-than-additive effect of CFZ on QTcF. We found no interaction between PRET and BDQ or CFZ. Our model can be used to assess the exposure-safety analysis of these drugs as part of other proposed drug regimens.

## 656 CLOFAZIMINE DRUG LEVELS AND CARDIAC TOXICITY IN CHILDREN WITH RIFAMPICIN-RESISTANT TB

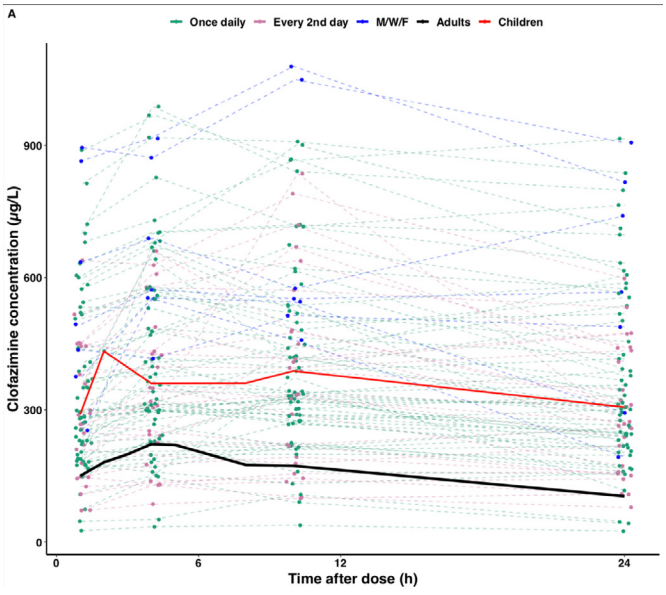
**Ali M. Ali**[1], Belen P. Solans[1], Jana Winckler[2], Anneke Hesseling[2], Heather Draper[2], Simon Schaaf[2], Louvina van der Laan[2], Jennifer Hughes[2], Anthony Garcia-Prats[2], Rada Savic[1]
*[1]University of California San Francisco, San Francisco, CA, USA, [2]Stellenbosch University, Stellenbosch, South Africa*

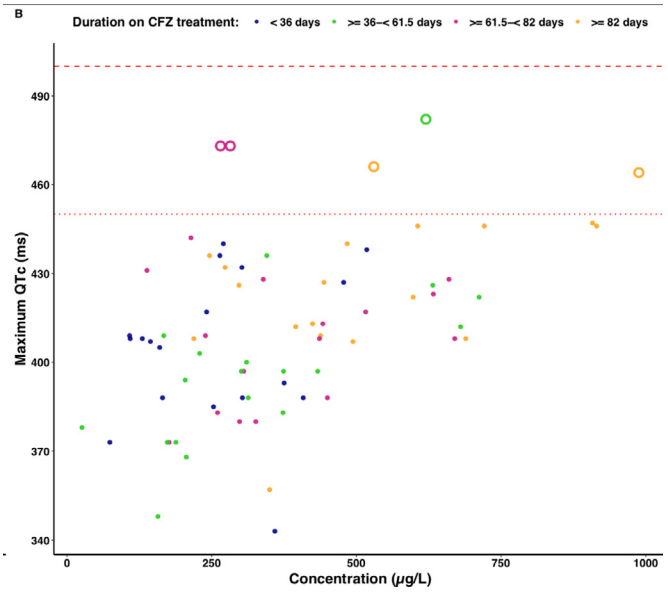
**Background:** Clofazimine (CFZ) is routinely recommended for rifampicin-resistant tuberculosis (RR-TB) treatment, but no pharmacokinetic (PK) and limited safety data are available in children. We aimed to characterize CFZ PK and its effect on QT prolongation in children with RR-TB.

**Methods:** An observational cohort study of South African children <18 years old treated for RR-TB with a multidrug regimen containing CFZ and other QT prolonging drugs such as moxifloxacin. CFZ 100mg gel caps, that could not be split, were used. PK sampling and electrocardiograms were done pre-dose and at 1-, 4- and 10-hours post-dose. Adult South African CFZ PK data (100mg daily dose) was used for comparison. CFZ PK was characterized using nonlinear mixed effect models. Linear regression related changes in corrected QT (Fridericia method, QTcF) and CFZ maximum concentrations ($C_{max}$).

**Results:** 54 and 78 children contributed PK and QTcF data, respectively. For the PK cohort, the median age and weight (2.5th-97.5th centiles) were 3.3 (0.4-16.1) years and 13.3 (6.3-55.7) kg, respectively. CFZ was given orally once daily (≥20 kg), or every 2nd day (10-20 kg), or Monday, Wednesday, and Friday (<10 kg) in 17 (31.5%), 26 (48.1%) and 11 (20.4%) children, respectively. The median (2.5th-97.5th) overall weekly dose was 25 (13-36) mg/kg. Median duration of CFZ treatment up to the maximum time of QTcF was 78 (24-474) days. Five (9.3%) children lived with HIV, 28 (51.9%) were female and 6 (11.1%) received open capsules. Median $C_{max}$ (2.5th-97.5th centile) of 490 (146-965) µg/L was reached at ~4.2 hours post-dose; adult CFZ $C_{max}$ of 338 (164-609 µg/L) was reached at 5 hours post-dose. One compartment model best described the PK data. Allometric scaling by weight was not supported by the data. Age significantly affected volume of distribution with a 30% increase per year. HIV+ children had 2-times higher CFZ clearance compared to HIV- children. Median (2.5th-97.5th) pre-dose QTcF was 389 (331-463) ms and maximum QTcF was 417 (368-482) ms, reached at 4.3 hours after dose. Every 200 µg/L increase in CFZ concentration related to a QTcF prolongation of 2ms.

**Conclusion:** Overall, observed CFZ $C_{max}$ in children were higher than in adults; this is expected given the formulation constraints and resultant high mg/kg doses in children; more information about exposures over the dosing interval are needed to improve comparisons. A higher clearance in HIV-positive children needs further evaluation. CFZ concentrations were associated with an increase in QTcF.






## 657 SEX DIFFERENCES IN RATES OF TUBERCULOSIS IN PEOPLE WITH HIV IN RIO DE JANEIRO, BRAZIL

**Lelia H. Chaisson**[1], Betina Durovni[2], Eileen P. Scully[3], Solange Cavalcante[2], Jonathan Golub[3], Richard E. Chaisson[3], Valeria Saraceni[4]
*[1]University of Illinois at Chicago, Chicago, IL, USA, [2]Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil, [3]The Johns Hopkins University, Baltimore, MD, USA, [4]Secretaria Municipal de Saúde do Rio de Janeiro, Rio de Janeiro, Brazil*

**Background:** Rates of tuberculosis (TB) are markedly different in adolescent and adult men and women, with a global 2:1 ratio of cases in males compared to females. These differences have been presumed to reflect social and behavioral factors, but recent studies suggest that genetic, immunologic, and hormonal factors impact human responses to TB and other infectious diseases. We sought to determine whether sex differences in TB were present in people living with HIV (PLHIV) in Rio de Janeiro, Brazil.

**Methods:** We used a probabilistic strategy to link data on HIV notifications, CD4 counts, viral loads, antiretroviral therapy (ART), TB notifications, and deaths from four national electronic registries maintained by the Brazilian Ministry of Health. We included all PLHIV in Rio de Janeiro City from 2010-2016, with follow-up through 2017. We followed patients from January 1, 2010 (or entry into care for those with incident HIV) until TB diagnosis or death. We calculated TB incidence rates (IR) per 100 person-years (pys) and IR ratios (IRR) comparing TB IRs of males to females. We performed analyses for 1) all prevalent and incident HIV patients from 2010-2016, stratified by ART (initiated/not initiated) and 2) people with incident HIV diagnosed from 2010-2016, stratified by baseline CD4 count and ART.

**Results:** Among 54,957 PLHIV in Rio from 2010-2016, TB incidence was higher among men than women overall (IR 1.04 vs. 0.84 per 100pys, IRR 1.24, 95%CI 1.15-1.34), regardless of ART status (Table). Among the 30,485 patients with incident HIV, men and women had similar baseline CD4 counts (median 403 vs. 414 cells/mm$_3$) and ages (median 33 vs. 35 years), though men had slightly higher baseline HIV viral loads (median log viral load 4.34 vs. 3.96, p<0.001). TB incidence was higher among men than women overall (1.49 vs. 1.06 per 100pys, IRR 1.40, 95%CI 1.25-1.57) and among those with low or unknown baseline CD4 counts. TB incidence was higher among men than women regardless of ART status (no ART: 2.47 vs. 1.65 per 100pys, IRR 1.50, 95%CI 1.29-1.74; initiated ART: 1.00 vs. 0.72 per 100pys, IRR 1.38, 95%CI 1.17-1.64).

**Conclusion:** In a population of PLHIV from a TB endemic area, we found that TB rates were higher in men than women, despite similar age and CD4 cell counts and a higher prevalence of socioeconomic risks in women. These data suggest that biologic sex differences in host responses to infections may decrease the risk of TB in women with HIV infection.

| | Total | Male | Female | IRR, male vs. female (95% CI) |
|---|---|---|---|---|
| **A. All PLHIV** | **N=54,957** | **N=35,880** | **N=19,077** | |
| TB incidence per 100 pys (95% CI) | 0.97 (0.95-1.01) | 1.04 (1.00-1.09) | 0.84 (0.78-0.90) | 1.24 (1.15-1.34) |
| TB incidence per 100 pys, no ART (95% CI) | 1.63 (1.54-1.73) | 1.88 (1.75-2.01) | 1.24 (1.12-1.38) | 1.51 (1.33-1.72) |
| TB incidence per 100 pys, initiated ART (95% CI) | 0.77 (0.73-0.80) | 0.80 (0.76-0.85) | 0.71 (0.65-0.77) | 1.13 (1.01-1.25) |
| **B. Incident HIV** | **N=30,485** | **N=20,958** | **N=9,527** | |
| TB incidence per 100 pys (95% CI) | 1.34 (1.28-1.41) | 1.49 (1.40-1.57) | 1.06 (0.96-1.17) | 1.40 (1.25-1.57) |
| TB incidence per 100 pys, CD4 ≤350 (95% CI) | 2.92 (2.68-3.18) | 3.42 (3.10-3.77) | 2.03 (1.72-2.41) | 1.68 (1.38-2.04) |
| TB incidence per 100 pys, CD4 351-500 (95% CI) | 0.92 (0.74-1.15) | 1.00 (0.76-1.31) | 0.79 (0.54-1.17) | 1.26 (0.79-2.01) |
| TB incidence per 100 pys, CD4 >500 (95% CI) | 0.69 (0.57-0.83) | 0.77 (0.61-0.96) | 0.57 (0.42-0.79) | 1.34 (0.91-1.98) |
| TB incidence per 100 pys, CD4 unknown (95% CI) | 1.15 (1.07-1.23) | 1.23 (1.14-1.33) | 0.95 (0.83-1.08) | 1.30 (1.11-1.52) |
| TB incidence per 100 pys, no ART (95% CI) | 2.19 (2.05-2.34) | 2.47 (2.29-2.67) | 1.65 (1.45-1.88) | 1.50 (1.29-1.38) |
| TB incidence per 100 pys, initiated ART (95% CI) | 0.91 (0.85-0.98) | 1.00 (0.92-1.09) | 0.72 (0.62-0.84) | 1.38 (1.17-1.64) |

## 658 SEX DIFFERENCES IN LATENT TUBERCULOSIS INFECTION AMONG CLOSE CONTACTS IN BRAZIL

**Paul Y. Wada**[1], Peter F. Rebeiro[1], Allyson Guimarães da Costa[2], Rebeca C. Araújo[2], Mariana Araújo-Pereira[3], Beatriz Barreto-Duarte[3], Alexandra B. Souza[2], Michael S. Rocha[4], Megan Turner[5], Valeria Cavalcanti Rolla[6], Afrânio L. Kritski[7], Marcelo Cordeiro-Santos[2], Bruno B. Andrade[3], Timothy Sterling[1]
*[1]Vanderbilt University, Nashville, TN, USA, [2]Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, Manaus, Brazil, [3]Instituto Gonçalo Moniz, Salvador, Brazil, [4]Instituto Brasileiro para Investigação da Tuberculose, Fundação José Silveira, Salvador, Brazil, [5]Vanderbilt University, Nashville, TN, USA, [6]Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, [7]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil*

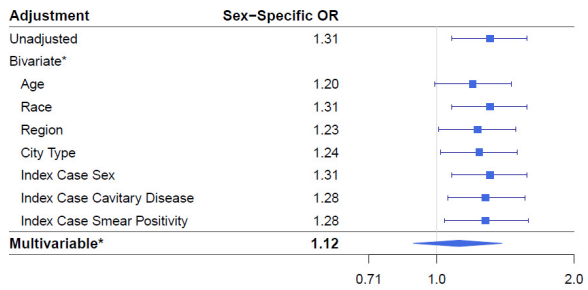
**Background:** Globally, more men than women develop and die of tuberculosis (TB). However, fewer data exist on possible sex disparities in latent TB infection (LTBI). We assessed for potential sex differences in LTBI acquisition among close TB contacts; based on preliminary data, we hypothesized that women were more likely than men to have LTBI.

**Methods:** Regional Prospective Observational Research for TB (RePORT) Brazil is an observational cohort study of culture-confirmed pulmonary TB and their close contacts. Participants were enrolled from five sites in three regions of Brazil (Rio de Janeiro, Salvador, and Manaus) from June 2015 -June 2019. Close contacts were followed for two years post-enrollment, with LTBI defined as a positive interferon-γ release assay (IGRA; QuantiFERON 3rd or 4th generation) at baseline or else at six months, if negative at baseline. Utilizing univariate, bivariate, and multivariable logistic regression models, we obtained unadjusted and adjusted odds ratios (OR) and their 95% confidence intervals (CI) for LTBI acquisition by birth sex among close contacts. Sensitivity analyses were performed to account for possible false positive assay conversion.

**Results:** Of 1838 close contacts, 1093 (59%) were women. A total of 504 (46%) women had a positive IGRA compared to 295 (40%) men: 433 (40%) vs. 246 (33%) at baseline and 71 (6%) vs. 49 (7%) at six months, respectively. The unadjusted OR for IGRA positivity among women vs. men was 1.31 (95% CI: 1.08-1.58), with little variation on sensitivity analysis. Bivariate adjustments for age, race, region, city type, index case sex, cavitary disease, and smear positivity yielded adjusted sex-specific ORs ranging from 1.20 to 1.31 (p-value range: 0.005-0.06). Final multivariable adjustment by age, region, city type, cavitary disease, and smear positivity simultaneously yielded a sex-specific OR of 1.12 (95% CI: 0.89-1.39; Figure 1).

**Conclusion:** The point estimate for LTBI among close TB contacts in Brazil was substantially higher in women, though it was no longer statistically significant after controlling for multiple potential confounders simultaneously. Notably, bivariate adjustments had a limited impact on the sex-specific effect size. An assessment in larger cohorts of close TB contacts with greater statistical power is warranted. If the sex disparity in LTBI is replicated, studies of underlying differences in TB pathogenesis could provide further context.

**Figure 1.** Forest plot for unadjusted, bivariate-adjusted, and multivariable-adjusted sex-specific odds ratios for IGRA positivity among close contacts of an index pulmonary TB source case




IGRA positivity was defined as a single positive QuantiFERON result at baseline or 6 months from enrollment.

Abbreviations: IGRA = interferon-γ release assay; OR = odds ratio; TB = tuberculosis.

*For bivariate adjusted OR, IGRA positivity was regressed on sex and the following factor. For multivariable adjusted OR, IGRA positivity was regressed on sex, age, city type, index cavitary disease, and index smear positivity.

## 659 MODELING THE IMPACT OF HIV AND TB INTERVENTIONS ON SOUTH AFRICAN TB TRENDS: 1990-2019

**Mmamapudi Kubjane**[1], Muhammad Osman[2], Rory Dunbar[2], Andrew Boulle[1], Leigh Johnson[1]

*[1]University of Cape Town, Cape Town, South Africa, [2]Stellenbosch University, Cape Town, South Africa*

**Background:** The South African tuberculosis (TB) epidemic is largely driven by HIV. Interventions including directly observed therapy (DOTS), antiretroviral therapy (ART), isoniazid preventative therapy (IPT), increased TB screening, and Xpert MTB/RIF have been implemented to reduce TB incidence and mortality. This study aimed to estimate the impact of HIV and interventions on the South African TB epidemic between 1990 and 2019.

**Methods:** An age-sex stratified dynamic TB transmission model for South Africa was developed. A Bayesian approach was used to calibrate the model to the numbers of people starting treatment from the electronic TB register, deaths from the vital register, microbiological tests, and a national TB prevalence survey. Counterfactual scenarios were simulated to estimate TB incidence and mortality attributable to HIV and tuberculosis incidence reductions due to the interventions mentioned above.

**Results:** Between 1990 and 2019, 8.0 million (95% confidence interval (CI) 7.7 million – 8.3 million) South African adults developed TB, and 2.1 million (95% CI 2 million – 2.2 million) died from TB. HIV accounted for 67.4% (95% CI 66.9% – 68%.0) of TB incidence and 76.4% (95% CI 75.5% – 77.3%) of TB mortality (Figure). Over the ten-year period 2009-2019, TB incidence and mortality declined by 35% and 45% respectively. Most of the reduction in TB incidence in 2019 was due to ART (25.2%, 95% CI 24.7% – 26.2%) and increased TB screening (25.0%, 95% CI 23.1% – 27.0%), while IPT and DOTS had a small effect and Xpert MTB/RIF had no significant effect. Despite the null effect on TB incidence, since its introduction in 2011, Xpert MTB/RIF reduced the number of individuals starting treatment on an empirical basis by 58% in 2019.

**Conclusion:** HIV has had a tremendous effect on TB incidence and mortality. The provision of ART and intensification of TB screening explain most declines in TB incidence between 2005 and 2019. Continued efforts are required to strengthen ART provision and tuberculosis screening to achieve substantial progress in meeting the End TB targets.

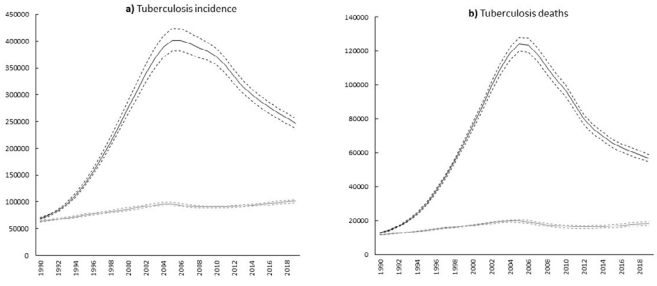



**Figure: The impact of HIV on tuberculosis incidence (a) and mortality (b) in adults (+15 years), 1990-2019.** The solid grey line represents the counterfactual scenario where there is no HIV assumed in the model. The solid black line represents the baseline scenario where HIV is present. The dashed lines represent 95% confidence intervals.

## 660 CLINICAL AND LABORATORY PREDICTORS OF TUBERCULOSIS RECURRENCE

New Investigator Scholar

**Clinical:**

**Sonya Krishnan**[1], Nikhil Gupte[1], Shreyas Desmukh[2], Padma Priyadarshini[3], Sanjay Gaikwad[4], Vijay Vishwanathan[5], Madhusudan Barthwal[6], Amita Gupta[1], Hardy Kornfeld[7], Jonathan Golub[1], Vidya Mave[2]

*[1]The Johns Hopkins University, Baltimore, MD, USA, [2]BJ Medical College Clinical Trials Unit, Pune, India, [3]National Institute for Research in Tuberculosis, Chennai, India, [4]Byramjee-Jeejeebhoy Government Medical College, Pune, India, [5]Maasstad Hospital, Rotterdam, Netherlands, [6]Dr. D.Y. Patil Medical College, Pune, India, [7]University of Massachusetts, Worcester, MA, USA*

**Background:** Despite successful completion of therapy for drug-susceptible pulmonary tuberculosis (PTB), a subset of individuals experience an unfavorable treatment outcome of tuberculosis (TB) recurrence. India accounts for 26% of the global burden of TB and few data on predictors of TB recurrence exist, especially with a focus on India. A TB recurrence prediction model could enable clinicians to identify patients at risk for recurrence during antituberculosis therapy (ATT) and may be used to alter patient care strategies, such as enhanced monitoring post treatment for high-risk individuals.

**Methods:** We conducted a retrospective analysis leveraging 3 NIH and Indian government funded observational TB cohorts in India (TB-DM, c-TRIUMPh, and eDOTS) designed to assess risk factors associated with unfavorable TB treatment outcomes. Adults newly diagnosed with PTB were enrolled and initiated on ATT, with 18-24 months of follow-up. A priori we selected 8 clinical and laboratory candidate predictors for recurrence based on previously published prediction models and expert opinion. We randomly selected 80% of the dataset and used multivariable logistic regression and bootstrapped backwards selection (repetitions=1000) to identify the best predictors of TB recurrence. We measured model accuracy by receiver operating characteristic (ROC) curve and area under the curve (AUC). We tested model fit by Akaike information criterion (AIC) and reliability by Kappa statistic. We internally validated the model with the remaining 20% of the dataset, generating the model accuracy, sensitivity, and specificity.

**Results:** Among 1164 adults diagnosed with PTB who completed ATT and achieved cure, 95 (8%) subsequently experienced recurrence. The most important predictors of TB recurrence were female sex, low body mass index (BMI), ever smoker history, month 2 (M2) smear positivity, and M2 culture positivity (Table 1). The model exhibited a c-statistic of 0.68 (95% CI 0.52-0.84) and a Kappa statistic of 0.23. Internal validation revealed an accuracy of 90% (95% CI 0.86-0.93), a sensitivity of 0.94 and a specificity of 0.31.

**Conclusion:** Our prediction modeling revealed female sex, low BMI, ever smoker history, M2 smear positivity, and M2 culture positivity as the most important predictors to discriminate TB recurrence from sustained cure.

**Table 1. Key clinical and laboratory variables from final model to predict tuberculosis recurrence.**

| Predictor Variable for Tuberculosis Recurrence* | Coefficient | Standard Error |
|---|---|---|
| Intercept | -2.10 | 0.70 |
| Female Sex | -0.56 | 0.30 |
| Ever smoker history (Yes) | -0.51 | 0.37 |
| Body mass index | -0.02 | 0.04 |
| Smear positivity (month 2) | 0.64 | 0.40 |
| Culture positivity (month 2) | 0.73 | 0.35 |
| Age | -- | -- |
| Alcohol use | -- | -- |
| Chest x-ray cavitation (month 6) | -- | -- |

*Key variables selected using multivariable logistic regression and bootstrapped backwards selection (repetitions=1000).

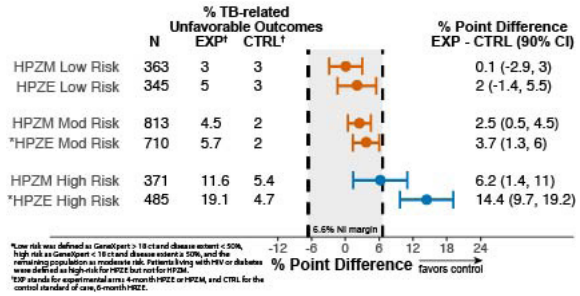
## 661 PATIENT-LEVEL POOLED ANALYSIS OF STUDY 31/A5349: A STRATIFIED MEDICINE APPROACH

**Vincent Chang**[1], Marjorie Z. Imperial[1], Patrick P. Phillips[1], Wendy Carr[2], Ekaterina Kurbatova[2], Andrew Vernon[2], Marc Weiner[3], Kelly Dooley[4], Susan Dorman[5], John Johnson[6], Susan Swindells[7], Richard E. Chaisson[4], Payam Nahid[1], Rada Savic[1]

*[1]University of California San Francisco, San Francisco, CA, USA, [2]Centers for Disease Control and Prevention, Atlanta, GA, USA, [3]University of Texas at San Antonio, San Antonio, TX, USA, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]Medical University of South Carolina, Charleston, SC, USA, [6]Case Western Reserve University, Cleveland, OH, USA, [7]University of Nebraska Medical Center, Omaha, NE, USA*

**Background:** Study 31/A5349 (NCT02410772) was a Phase III randomized controlled trial assessing 4-month regimens of once-daily isoniazid, rifapentine, and pyrazinamide plus moxifloxacin (HPZM) or ethambutol (HPZE) compared

to the 6-month HZE + rifampicin standard treatment for drug-sensitive tuberculosis (TB). While HPZM arm successfully demonstrated noninferiority, HPZE arm did not. Nonetheless, 82% of participants receiving HPZE were cured. Through a pooled analysis of patient-level data, we define phenotypes that are hard to treat and populations that might also be treated with 4-month HPZE.
**Methods:** We included 2343 patients in the microbiologically eligible population from all arms in the analysis. Parametric survival analysis identified significant predictors for TB-related unfavorable outcomes, which were used to define low, moderate, and high-risk groups. Post hoc noninferiority analyses were performed on HPZE and HPZM regimens stratified by risk group.
**Results:** Major risk factors for TB-related unfavorable outcomes in both experimental arms were rifapentine exposure and baseline disease burden, as measured by GeneXpert cycle threshold and disease extent on chest x-ray. Low risk was defined as GeneXpert > 18 ct and disease extent < 50%, high risk as GeneXpert < 18 ct and disease extent ≥ 50%, and the remaining population as moderate risk. In HPZE arm only, patients with HIV or diabetes were at higher risk of unfavorable outcomes compared to HIV-negative or non-diabetic patients (HIV: 16.1% unfavorable outcomes vs 8.9%, HR = 1.95 (95% CI: 1.03, 3.7); Diabetes: 43% vs 8.9%, HR = 6.53 (CI: 2.8, 15)). Therefore, patients living with HIV or diabetes were included in the high-risk group for HPZE. Post hoc noninferiority analyses of HPZM and HPZE regimens stratified by risk group demonstrated noninferiority in low and moderate risk groups, while neither experimental regimen demonstrated noninferiority in the high-risk groups (Fig 1).
**Conclusion:** Low and moderate risk groups, which constitute the vast majority (73.6%) of all participants, had noninferior outcomes with 4-month HPZM and HPZE in this post hoc analysis, despite failure of HPZE to demonstrate noninferiority in primary analysis. Outcomes in individuals at high risk can potentially be improved further. Strong relationship with rifapentine exposure suggests that further dose optimization might lead to increased cure rates in patients at highest risk and ultrashort (2 or 3 months) durations for low/moderate risk groups.




## 662 LATENT TB INFECTION TREATMENT ACCELERATES IMMUNE RECOVERY AMONG PLWH ON ART

**Eduarda Grinsztejn**[1], Luciane Velasque[2], Sandra Wagner-Cardoso[2], Brenda Hoagland[2], Sandro Nazer[2], Beatriz Grinsztejn[2], Valdilea Veloso[2]
*[1]Case Western Reserve University, Cleveland, OH, USA, [2]Instituto Nacional de Infectologia Evandro Chagas - Fiocruz, Rio de Janeiro, Brazil*

**Background:** In PLWH, both active and latent TB co-infections are associated with immune activation that correlate with HIV progression and mortality. CD4/CD8 ratio <1 is predictive of non-AIDS-related morbimortality. We aimed to evaluate the impact of latent TB infection (LTBI) treatment and prior/concomitant TB co-infection at time of ART initiation in time to CD4/CD8 ratio normalization in a cohort of cisgender men who have sex with men (cis-MSM) and transgender women (TGW) from Rio de Janeiro, Brazil, who initiated ART during acute HIV infection (AHI), recent HIV infection (RHI) and chronic HIV infection (CHI).
**Methods:** This observational prospective study evaluated time from ART initiation to CD4/CD8 ratio normalization (CD4/CD8 ratio≥1) in a cohort of cis-MSM/TGW with AHI/RHI and CHI. Cox proportional hazards regression models were fitted to estimate predictors, hazards ratio and 95% confidence intervals of time to CD4/CD8 ratio≥1.
**Results:** A total of 550 patients were enrolled: 65 (12%) AHI, 35 (6%) RHI and 450 (82%) CHI, of which 257 had baseline CD4≥350 cells/mm$_3$ and 193 <350 cells/mm$_3$. Median time to CD4/CD8 normalization in AHI was 5.6 months (1.1-16.8), RHI 7 months (2.5-40.8), CHI 21 months (13-37) and 25.3 months (14.8-38.5) among those with CD4≥350 cells/mm$_3$ and <350 cells/mm$_3$, respectively. Seven individuals used chemoprophylaxis in the AHI group, 6 in the RHI, 28 in the CHI with CD4≥350 cells/mm$_3$ and 28 in the CHI with CD4<350 cells/mm$_3$. Overall, 28 individuals had previous or concomitant TB at time of ART initiation, all of those were chronically infected (4 with CD4≥350 cells/mm$_3$; 24 with CD4<350 cells/mm$_3$). In the multivariate model, AHI was associated with fastest immune recovery (HR 6.03 3.70-9.82 p<0.001), followed by RHI (HR 4.47 2.57-7.76 p<0.001) and CHI with CD4≥350 cells/mm$_3$ (HR 1.87 1.24-2.84 p=0.003), compared to CHI with CD4<350 cells/mm$_3$. LTBI treatment was significantly associated with shorter time to CD4/CD8 ratio normalization (HR 1.79 1.22-2.62 p=0.003). Conversely, individuals who had TB prior or concomitantly to ART initiation had longer time to CD4/CD8 ratio normalization (HR 0.41 0.16-1.02 p=0.054).
**Conclusion:** Prior or concomitant TB at ART initiation delays immune recovery, whereas LTBI treatment accelerates immune recovery. Beyond preventing TB occurrence, LTBI treatment is critical to maximize ART benefits in low- and middle- income countries, where TB remains the leading cause of HIV-related morbidity and mortality.

Unadjusted and adjusted hazard ratios and 95% confidence intervals for time to CD4/CD8 ratio normalization

| Variable | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | HR (CI 95%) | p-value | HR (CI 95%) | p-value |
| CHI with CD4<350 | 1.(ref.) | | 1.(ref.) | |
| CHI with CD4≥350 | 2.05 (1.37-3.07) | 0.001 | 1.87 (1.24-2.84) | 0.003 |
| RHI | 5.21 (3.03-8.96) | <0.001 | 4.47 (2.57-7.76) | <0.001 |
| AHI | 6.97 (4.33-11.24) | <0.001 | 6.03 (3.70-9.82) | <0.001 |
| Age per10-year increase | 0.87 (0.73-1.04) | 0.123 | --- | |
| Black/Mixed vs White | 1.29 (0.96-1.77) | 0.122 | --- | |
| Cis-MSM vs TGW | 1.06 (0.75-1.48) | 0.753 | --- | |
| Schooling <12years vs ≥12years | 1.14 (0.80-1.61) | 0.475 | --- | |
| Viral Load log$_{10}$ copies/mL | 1.10 (0.97-1.26) | 0.144 | --- | |
| Prior/concomitant TB | 0.33 (0.16-0.67) | 0.002 | 0.41 (0.16-1.02) | 0.054 |
| LTBI treatment | 1.80 (1.24-2.59) | 0.002 | 1.79 (1.22-2.62) | 0.003 |

Abbreviations: AHI acute HIV infection; RHI recent HIV infection; CHI chronic HIV infection; cis-MSM cisgender men who have sex with men; TGW transgender women; TB tuberculosis; LTBI latent TB infection

## 663 THE DREAMM PROJECT: EPIDEMIOLOGICAL FINDINGS AND CRYPTOCOCCAL MENINGITIS OUTCOMES

**Cecelia Kanyama**[1], Charles Kouanfack[2], Sayoki Mfinanga[3], Saulos Nyirenda[4], Aude Sturny-Leclere[5], Emma Beaumont[6], Sokoine Lesikari[3], Timothée Boyer-Chammard[5], Olivier Lortholary[5], Shabbar Jaffar[7], John Bradley[6], Sile Molloy[8], Tom Harrison[8], Angela Loyse[8]
*[1]University of North Carolina Project–Malawi, Lilongwe, Malawi, [2]University of Dshang, Dschang, Cameroon, [3]National Institute for Medical Research – Muhimbili Centre, Dar es Salaam, Tanzania, United Republic Of, [4]Zomba Central Hospital, Zomba, Malawi, [5]Institut Pasteur, Paris, France, [6]London School of Hygiene & Tropical Medicine, London, UK, [7]Liverpool School of Tropical Medicine, Liverpool, UK, [8]St George's University of London, London, UK*

**Background:** Central nervous system (CNS) infection leads to approximately one third of HIV-related deaths in African low-and middle-income countries. There is an urgent need to implement new WHO treatment regimens for cryptococcal meningitis, and determine the epidemiology of HIV-related CNS infection. DREAMM is an implementation science project designed to prospectively determine the epidemiology and reduce the mortality of HIV-related CNS infection in Tanzania, Malawi and Cameroon.
**Methods:** DREAMM is divided into 3 phases: Observation, Training, and Implementation in five public hospitals. The main DREAMM intervention is the implementation of an algorithm for HIV-related CNS infection using two implementation strategies : 1) Empowerment of local leadership, and 2) Quality improvement in delivery of hospital care. Prevalence of the main causes of HIV-related CNS infection (cryptococcal, tuberculous, and bacterial meningitis and cerebral toxoplasmosis) in the implementation phase are expressed as proportions and presented overall and by country.
**Results:** 356 participants with suspected HIV-related CNS infection were enrolled in the implementation phase. After investigation, 76% (95% CI: 71-80), 270/356 had a confirmed or probable CNS infection. Of these, cryptococcal meningitis was the leading cause in Malawi (67% (95% CI: 55-77), 54/81) and

Tanzania (60% (95% CI: 49-69), 59/99), followed by bacterial meningitis (17% (95% CI: 10-27), 14/81) in Malawi and tuberculous meningitis (33% (95% CI: 24-44), 33/99) in Tanzania. In Cameroon, cerebral toxoplasmosis (44% (95% CI: 34-55), 40/90) and cryptococcal meningitis 40% (95% CI: 30-51), 36/90) were leading causes. Overall, 2- and 10-week all-cause mortality for cryptococcal meningitis was 23% (95% CI: 12-31), 34/148, and 45% (95% CI: 37-53), 66/147, respectively. For those who received 1-week amphotericin B plus flucytosine 2- and 10-week mortality was 22% (95% CI:14-33), 20/89, and 47% (95% CI: 37-58), 42/89, respectively, and among those receiving 2 weeks' fluconazole plus flucytosine, 2- and 10-week mortality was 22% (95% CI: 11-37), 10/45 and 38% (95% CI: 24-53), 17/45 respectively.

**Conclusion:** Two-week outcomes comparable to those from clinical trials are attainable for cryptococcal meningitis following implementation of DREAMM in routine care. DREAMM epidemiological data will assist Ministries of Health, non-governmental organisations and global funders in implementing specific packages of care for HIV-related CNS infection to save lives.

## 664 COST-EFFECTIVENESS OF THE AMBITION REGIMEN FOR HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS

**Charles Muthoga**[1], David S. Lawrence[2], David Meya[3], Henry Mwandumba[4], Cecelia Kanyama[5], Graeme Meintjes[6], Conrad Muzoora[3], Mosepele Mosepele[7], Chiratidzo E. Ndhlovu[8], Tinevimbo Shiri[9], Shabbar Jaffar[9], Tom Harrison[10], Joseph N. Jarvis[2], Louis W. Niessen[9]

*[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]London School of Hygiene & Tropical Medicine, London, UK, [3]Infectious Disease Institute, Kampala, Uganda, [4]Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi, [5]University of North Carolina Project–Malawi, Lilongwe, Malawi, [6]Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa, [7]University of Botswana, Gaborone, Botswana, [8]University of Zimbabwe, Harare, Zimbabwe, [9]Liverpool School of Tropical Medicine, Liverpool, UK, [10]St George's University of London, London, UK*

**Background:** HIV-associated cryptococcal meningitis remains a key driver of AIDS-related mortality. The AMBITION-cm phase III clinical trial demonstrated that a single, high-dose of liposomal amphotericin B (L-AmB) given on a flucytosine and fluconazole backbone was non-inferior to the WHO recommended treatment of 7 daily doses of amphotericin B deoxycholate plus flucytosine followed by 7 days of fluconazole and was associated with significantly fewer adverse events. Here we present a cost-effectiveness analysis of this approach in five countries.

**Methods:** 814 participants were randomised 1:1 to either L-AmB (n= 407) or control (n= 407) regimens in Botswana, Malawi, South Africa, Uganda and Zimbabwe. We collected individual resource use data and health outcomes for each participant. Costing data from each country setting was also collected. Health outcomes were calculated in life years (LY) gained. The Malawian context was chosen for the primary analysis. Mean costs, cost-differences and an incremental cost effectiveness ratio were calculated. A probabilistic analysis was performed using non-parametric bootstrapping. Additional scenarios were explored based on an implementation laboratory monitoring schedule, the potential for the L-AmB arm to reduce the length of hospital admission, and fluctuations in antifungal prices.

**Results:** Mortality risk in the L-AmB group was 24.8% (95% CI; 20.7% - 29.3%) and in the control group was 28.7% (95% CI; 24.4% - 33.4%) with a risk difference of -3.9% (95 CI; -10.0% - 2.2%). Using Malawi as the reference country, the mean per patient total costs were 2021 US$1369 (95% CI; $1314 - $1424) in the L-AmB arm and 2021 US$1237 (95% CI; $1181 - $1293) in the control arm. The mean incremental cost-effectiveness ratio (ICER) was 2021 US$128 (95% CI $53 - $257) per LY gained. The results were similar across countries. Using a real-world laboratory monitoring schedule, the mean ICER cost per LY gained reduced to 2021 US$80 (95% CI $15 - $275). In countries where hospital admission costs were high (Botswana and South Africa), L-AmB treatment showed cost-savings if patients could be discharged one or two days earlier, respectively.

**Conclusion:** The single, high-dose L-AmB regimen was cost-effective in comparison to the current WHO recommended standard of care and this effect is likely to be greater in real-world implementation. There is an urgent need to broaden access to L-AmB and flucytosine.

**Table 1:** Cost-effectiveness analyses for the AMBITION trial for each site based on in-trial resource use and potential real-world resource use

| Treatment arm | Mean (95% CI) in-trial treatment costs per patient (2021 US$) | Incremental Cost-Effectiveness Ratio of L-AmB treatment (2021 US$/LY Gained) | | Break-even analyses of hospital costs and admission days for L-AmB regimen (probable real-world resource use) | |
|---|---|---|---|---|---|
| | | In-trial resource use | Probable real-world resource use | Hospital cost per day (2021 US$) | Number of admission days required to break-even |
| **Malawi** | | | | | |
| Control | 1237 (1181 - 1293) | Reference | Reference | 18.36 | 5 |
| L-AmB | 1369 (1314 - 1424) | 128 (53 - 257) | 80 (15 - 275) | | |
| **Botswana** | | | | | |
| Control | 2049 (1939 - 2158) | Reference | Reference | 88.80 | 1 |
| L-AmB | 2164 (2049 - 2280) | 92 (53 -221) | 71 (40 - 182) | | |
| **South Africa** | | | | | |
| Control | 1858 (1761 - 1956) | Reference | Reference | 80.66 | 2 |
| L-AmB | 1994 (1890 - 2097) | 130 (65 - 251) | 101 (80 -140) | | |
| **Uganda** | | | | | |
| Control | 628 (604 - 652) | Reference | Reference | 13.85 | 9 |
| L-AmB | 748 (723 - 772) | 143 (85 - 217) | 121 (55 - 231) | | |
| **Zimbabwe** | | | | | |
| Control | 760 (731 - 788) | Reference | Reference | 15.90 | 7 |
| L-AmB | 857 (828 - 887) | 152 (36 - 381) | 106 (17 - 328) | | |

## 665 RAPID SEMI-QUANTITATIVE ANTIGEN TESTING AND MORTALITY IN CRYPTOCOCCAL MENINGITIS

**Tshepo B. Leeme**[1], Kwana Lechiile[1], Cheusisime Kajanga[2], Melanie Moyo[2], Henry Mwandumba[2], Nabila Youssouf[3], Mosepele Mosepele[4], Tshepiso Mbangiwa[1], Alexandre Alanio[5], Aude Sturny-Leclere[5], Timothée Boyer-Chammard[5], Olivier Lortholary[5], David S. Lawrence[3], Tom Harrison[6], Joseph N. Jarvis[1]

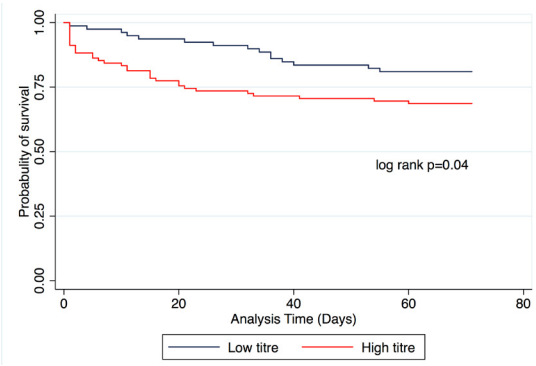
*[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi, [3]London School of Hygiene & Tropical Medicine, London, UK, [4]University of Botswana, Gaborone, Botswana, [5]Institut Pasteur, Paris, France, [6]St George's University of London, London, UK*

**Background:** Mortality rates in individuals with HIV-associated cryptococcal meningitis (CM) remain high in sub-Saharan Africa, with 25-50% of individuals dying within 10 weeks of diagnosis despite antifungal therapy. Stratifying patients with CM into higher and lower risk groups could help guide management and target at-risk individuals for more intensive care. The BIOSYNEX® CryptoPS is a semi-quantitative, lateral flow immunochromatic test designed for the detection and quantification of cryptococcal antigen (CrAg) in bloods and cerebrospinal fluid (CSF), and may have value as both a diagnostic and a prognostic tool. We performed a study to determine the utility of BIOSYNEX® CryptoPS testing in individuals presenting with CM in Botswana and Malawi.

**Methods:** From January 2018 to February 2021, EDTA whole blood specimen were collected from patients admitted with CM and included in the AMBITION-cm clinical trial in Botswana (Princess Marina Hospital, Gaborone) and Malawi (Queen Elizabeth Hospital, Blantyre). CrAg detection and quantification were performed using the BIOSYNEX® CryptoPS according to manufacturer's instruction, with individuals classified as negative, low titer, or high titer. We determined associations between CryptoPS titers and baseline variables, and used Cox regression to explore the relationship between CryptoPS titer and 10-week mortality.

**Results:** We tested 187 individuals presenting with CM using the BIOSYNEX® CryptoPS on whole blood. 181 of 187 (97%) were CryptoPS positive; 79/181 (44%) had a low titer, and 102/181 (56%) had a high titer. Individuals with high CryptoPS titers had significantly lower mean CD4 counts (53 cells/$mm_3$ vs 69 cells/$mm_3$, p= 0.016) and higher mean CSF fungal burdens (1,569,279 CFU/mL vs 169,247 CFU/mL, p<0.0001) than those with low titers. Over 10 weeks of follow-up, 32/102 (31%) of those with high titers died compared to 15/79 (19%) with low titers [HR 1.88, 95% confidence interval 1.02-3.47, p=0.04]. This mortality difference remained significant after adjustment for age, sex, and treatment group.

**Conclusion:** The BIOSYNEX® CryptoPS semi-quantitative CrAg assay provides useful prognostic information in individuals presenting with HIV-associated cryptococcal meningitis. Individuals with high blood CryptoPS titers had higher baseline fungal burdens in the CSF and were almost twice as likely to die as those with low titers.




## 666 ACTG A5351S: EFFECT OF IMMUNE-MODULATORY INTERVENTIONS ON CMV REPLICATION DURING ART

New Investigator Scholar

**Elizabeth Hastie**[1], Carlee B. Moser[2], Xin Sun[2], Jeff L. Lennox[3], Priscilla Hsue[4], Ronald J. Bosch[2], Steven G. Deeks[4], Milenka Vargas[1], Michael M. Lederman[5], Peter W. Hunt[4], Timothy J. Henrich[4], Vincent Marconi[3], Sara Gianella[1]
*[1]University of California San Diego, San Diego, CA, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Emory University, Atlanta, GA, USA, [4]University of California San Francisco, San Francisco, CA, USA, [5]Case Western Reserve University, Cleveland, OH, USA*

**Background:** Two trials explored the effect of immune-modulators on inflammation in people with HIV (PWH) on suppressive ART. A5336 (ruxolitinib vs placebo) revealed decreased immune activation (sCD14, CD38+HDR+ on CD4+ T Cells) and cell survival (Bcl-2). A5337 (sirolimus, single arm) revealed decreased cellular cycling (Ki67+) and CD4+ T-cell HIV DNA. Here, we investigate if these immune-modulators affect CMV DNA to elucidate a possible contributing effect of CMV replication on inflammatory outcomes.

**Methods:** A subset of participants from A5336 (N=36, 509 samples) and A5337 (N=8, 126 samples) were co-enrolled in this study (A5351s). Genital secretions, oral swabs, and urine were assayed for CMV DNA by qPCR at baseline and longitudinally (5 timepoints over 12 weeks for A5336; 6 timepoints over 44 weeks for A5337). Immunological biomarkers from A5336 included IL-6, sCD14, Ki67+, and CD38+HLA-DR+ on T-cells. Correlations between CMV DNA and biomarkers were examined at study entry and week 5 and 10 by Spearman's correlations.

**Results:** Median participant age was 49 years (range: 25-62), 77% were male sex (at birth) and 47% black race, non-Hispanic. Median baseline CD4+ T-cells were 859 cells/mm$_3$. CMV DNA was detected in 45 genital (29%), 19 oral (11%), and 31 urine (18%) samples and was more commonly detected in men than in women (31% vs 3%). There was no apparent effect of either immune-modulatory intervention on CMV DNA (detectability or levels) at any mucosal site over time or between arms (all P values >0.1). Detectable CMV DNA in all post-baseline time points in A5336 was 25% in the placebo arm and 31% in the ruxolitinib arm (genital secretion), 8% and 13% (oral swabs), and 24% and 15% (urine). Similarly, no difference in CMV DNA was found pre and post Sirolimus for A5337. Within A5336, there was a consistent positive association between CMV DNA and Ki67+ on CD4+ and CD8+ T-cells (r between 0.30-0.62) and CD38+HLA-DR+CD8+ T-cells (r between 0.31-0.37) at multiple time points and from multiple sample sites (see Table 1).

**Conclusion:** Our pilot study did not observe any significant effect of immune-modulators on CMV DNA in PWH on ART with high baseline CD4+ T-cells. We did observe a consistent association between CMV levels and immune activation and cycling of CD4+ and CD8+ T-cells, which could have implications for HIV persistence (through expansion of CD4+ T-cells) and HIV-associated morbidity (through expansion of CD8+ T-cells as lower CD4+/CD8+ T-cell ratio is predictive of poor clinical outcome).

| | | Genital Swab | | | Oral Swab | | | Urine Sample | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | r | P-value | N | r | P-value | N | r | P-value |
| IL-6 | Entry | 29 | 0.03 | 0.86 | 35 | 0.01 | 0.96 | 35 | 0.14 | 0.43 |
| | Week 5 | 28 | -0.34 | 0.08 | 33 | 0.04 | 0.81 | 30 | -0.25 | 0.18 |
| | Week 10 | 27 | -0.04 | 0.83 | 32 | 0.23 | 0.21 | 32 | 0 | 1.0 |
| sCD14 | Entry | 29 | 0.13 | 0.51 | 35 | **0.34** | **0.04** | 35 | 0.07 | 0.71 |
| | Week 5 | 28 | 0 | 1.0 | 33 | **0.38** | **0.03** | 30 | 0.09 | 0.65 |
| | Week 10 | 28 | -0.01 | 0.95 | 34 | 0.09 | 0.63 | 34 | 0.25 | 0.15 |
| (CD3+CD4+) Ki67+ | Entry | 26 | **0.31** | **0.13** | 32 | **0.33** | **0.07** | 32 | 0.18 | 0.32 |
| | Week 5 | 28 | **0.34** | **0.08** | 33 | 0.17 | 0.36 | 30 | **0.30** | **0.10** |
| | Week 10 | 27 | 0.11 | 0.58 | 33 | 0.14 | 0.43 | 33 | -0.07 | 0.70 |
| (CD3+CD8+) Ki67+ | Entry | 26 | **0.62** | **<0.01** | 32 | **0.48** | **0.01** | 32 | **0.35** | **0.05** |
| | Week 5 | 28 | **0.42** | **0.03** | 33 | 0.18 | 0.31 | 30 | **0.45** | **0.01** |
| | Week 10 | 27 | 0.28 | 0.16 | 33 | **0.48** | **<0.01** | 33 | 0.26 | 0.14 |
| (CD4+) CD38+HLADR+ | Entry | 26 | 0.26 | 0.20 | 32 | 0.27 | 0.13 | 32 | 0.19 | 0.31 |
| | Week 5 | 28 | 0.23 | 0.24 | 33 | **0.45** | **<0.01** | 30 | 0.18 | 0.35 |
| | Week 10 | 27 | 0.14 | 0.50 | 33 | 0.23 | 0.19 | 33 | -0.02 | 0.92el |
| (CD8+) CD38+HLADR+ | Entry | 26 | 0.29 | 0.15 | 32 | **0.32** | **0.07** | 32 | 0.20 | 0.28 |
| | Week 5 | 28 | 0.20 | 0.31 | 33 | **0.37** | **0.03** | 30 | **0.31** | **0.10** |
| | Week 10 | 27 | **0.35** | **0.07** | 33 | 0.29 | 0.10 | 33 | 0.18 | 0.32 |

**Table 1.** Association between CMV DNA level obtained from three different sites and serum inflammatory biomarkers in A5336 participants at three timepoints: entry, week 5, and week 10. Spearman correlations ≥ 0.30 bolded. Abbreviations: IL-6, interleukin-6; sCD14, soluble CD14; human leukocyte antigen DR, HLADR.

## 667 CYTOMEGALOVIRUS VIREMIA AS A RISK FACTOR FOR MORTALITY IN HIV-ASSOCIATED MENINGITIS

**Caleb Skipper**[1], Katherine Hullsiek[1], Kiiza Tadeo[2], Michael Okirwoth[2], Nelmary Hernandez-Alvarado[1], Claudia Fernandez-Alarcon[1], Emily Martyn[3], Jayne Ellis[3], Kenneth Ssebambulidde[2], Lillian Tugume[2], Edwin Nuwagira[2], Fiona Cresswell[3], David Meya[2], David R. Boulware[1], Mark R. Schleiss[1]
*[1]University of Minnesota, Minneapolis, MN, USA, [2]Infectious Diseases Institute, Kampala, Uganda, [3]London School of Hygiene & Tropical Medicine, London, UK*

**Background:** Cytomegalovirus (CMV) viremia is associated with increased mortality in persons with HIV. We previously demonstrated that CMV viremia was a risk factor for 10-week mortality in antiretroviral therapy (ART)-naïve persons with cryptococcal meningitis. We investigated whether similar observations existed over a broader cohort of HIV-associated meningitis.

**Methods:** We prospectively enrolled Ugandans with cryptococcal or tuberculous (TB) meningitis into clinical trials during 2015–2019. We quantified CMV DNA concentrations from stored baseline plasma or serum samples from 242 participants. We compared 18-week survival between those with and without CMV viremia.

**Results:** We included 211 persons with cryptococcal meningitis and 31 with TB meningitis, of whom a total of 86 (36%) had detectable CMV DNA. Baseline CD4+ T cell counts (15 vs. 20 cells/μL; P=0.21) and antiretroviral exposure (49% vs. 42%; P=0.33) were similar between CMV viremic and non-viremic persons, respectively. The 18-week mortality was 49% (42/86) in those with CMV viremia versus 32% (50/156) in those without (P=0.01) (Figure 1). Both any detectable CMV viremia (Hazard Ratio=1.66; 95%CI, 1.10–2.51; P=0.02) and increasing viral load (Hazard Ratio=1.22 per log$_{10}$ IU/mL increase; 95%CI, 1.09–1.37; P=0.007) were positively associated with all-cause mortality, which remained significant after multivariate adjustment.

**Conclusion:** CMV viremia was associated with a two-thirds higher risk of death at 18 weeks among persons with cryptococcal or TB meningitis. Further investigation is warranted to determine if CMV is a modifiable risk contributing to deaths in HIV-associated meningitis, versus its presence representing a sensitive biomarker of overall immune dysfunction.

**Figure 1. Survival Curve by CMV Viremia Status at 18 Weeks**

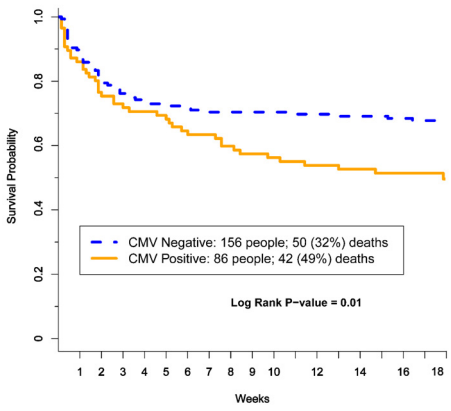



**Figure 1.** Kaplan-Meier curve comparing survival at 18 weeks. Persons with CMV viremia were more likely to die at 18 weeks as compared to persons without CMV viremia. Four participants were right-hand censored. This model does not include any multivariate adjustments. P-value was calculated by log-rank testing.

## 668 CMV VIREMIA AND DISEASE IN VERY ADVANCED LATE PRESENTERS: AN ADVANZ-4 TRIAL SUBSTUDY

New Investigator Scholar

**Paula Suanzes**[1], Adrià Curran[1], Ferran Torres[2], Maria A. Marcos[2], Pere Domingo[3], María Saumoy[4], Roger Paredes[5], Christian Manzardo[2], Lluis Force[6], Eva Bonfill[2], Nuria Climent[2], Montserrat Plana[2], Vicenç Falcó[1], Jose M. Miro[2]
*[1]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [2]Hospital Clinic of Barcelona, Barcelona, Spain, [3]Hospital de Sant Pau, Barcelona, Spain, [4]Hospital Universitario de Bellvitge, Barcelona, Spain, [5]Hospital Germans Trias i Pujol, Barcelona, Spain, [6]Hospital de Mataró, Mataró, Spain*

**Background:** The incidence of cytomegalovirus (CMV) end-organ disease (EOD) in patients with advanced HIV infection has dropped dramatically since the introduction of antiretroviral treatment (ART). In early studies CMV viremia was identified as a predictor of worse prognosis. Data regarding the clinical and immunological significance of CMV viremia in the era of new generation ART are still missing.
**Methods:** The Advanz-4 trial (NCT02337322) is a multicenter, randomized clinical trial that included 104 ART-naïve HIV-1 infected patients with <100 CD4+ T-lymphocytes (TL)/mm$_3$ randomly assigned 1:1 to receive DTG or DRV/r plus ABC+3TC. Patients were followed up for 48 weeks. We measured plasma CMV viral load (VL) by quantitative PCR and CMV-specific IgG/IgM at baseline (BL). The primary endpoint was the incidence of CMV EOD. Secondary endpoints were the proportion of patients with undetectable HIV VL, IRIS, inflammation markers, immune activation, HIV disease progression and death. Anti-CMV treatment was left to the discretion of the treating physician. A mITT analysis was done (3 patients in the DRV/r arm were excluded, none started the study medication). Statistical analysis was performed using SAS v9.4.
**Results:** At BL 43 (42.6%) participants had detectable CMV VL (DCV) (median:386 IU/mL, IQR:77-2130). There were no differences in BL CMV VL between ART arms (p=1.000). Clinical, immunological and virological features are depicted in the table. Eight (7.9%) patients developed CMV EOD (5 with unmasking CMV-related IRIS): 3 multiorgan involvement (including retinitis), 2 gastrointestinal infections, 1 myelitis, 1 pneumonitis, 1 CMV syndrome. Only 1 patient died (not CMV-related). BL HIV VL was higher in the DCV group, but there were no differences in BL CD4+TL values. At week 48, there was a lower proportion of patients with undetectable HIV VL in the DCV group but a greater increase in CD4+TL values. All the 11 cases of IRIS and most of the new AIDS events occurred in the DCV group. Inflammation (TNF-α, IL-6, hsCRP), immune activation (CD8+CD38+TL, CD8+CD38+DR+) markers were similar at BL and declined similarly in both groups (p>0.05 for all comparisons).
**Conclusion:** Although the incidence of CMV EOD in patients with advanced HIV infection is low, CMV viremia seems to be associated with a worse immunovirological situation and a higher rate of IRIS and AIDS events, probably marking a deeper degree of immunosuppression. We found no association between CMV viremia and inflammation or immune activation.

| mITT analysis | Total (n=101) | Detectable CMV viremia (n=43) | Undetectable CMV viremia (n=58) | p-value |
|---|---|---|---|---|
| Age, years, median (IQR) | 41 (31-47) | 41 (32-52) | 38.5 (31-47) | 0.460 |
| Sex, female, n (%) | 14 (13.9) | 6 (14.9) | 8 (13.8) | 1.000 |
| Baseline AIDS-defining event, n (%) | 42 (41.6) | 22 (51.2) | 20 (34.5) | 0.100 |
| Baseline HIV VL, copies/mL, median (IQR) | 367643.5 (79146-1245000) | 824869.5 (272000-2270000) | 173100 (65702-804000) | 0.001 |
| Baseline CMV-specific IgG positive, n (%) | 96 (95.05) | 43 (100.00) | 53 (91.38) | 0.070 |
| Baseline CD4+ TL, cells/mm3, median (IQR) | 33.5 (10.5-67.5) | 22 (10-48.3) | 38 (17.4-74.1) | 0.056 |
| Week 48 CD4+ TL, cells/mm3, median (IQR) | 226 (162.5-326) | 282 (182-377) | 200 (132-292.8) | 0.004 |
| Week 48 HIV VL <50 copies/mL, n (%) | 71 (70.3) | 24 (66.7) | 47 (88.7) | 0.016 |
| IRIS, n (%) | 11 (10.9) | 11 (25.6) | 0 (0) | <0.001 |
| CMV-related IRIS, n (%) | 5 (4.9) | 5 (11.6) | 0 (0) | 0.028 |
| New AIDS event, n (%) | 9 (8.9) | 7 (16.3) | 2 (3.5) | 0.035 |

## 669 A MORE INDIVIDUALIZED ANTIFUNGAL TREATMENT REGIMEN FOR MODERATE TO SEVERE HIV/PCP

**Yinqiu Huang**[1], Xiaoqing He[1]
*[1]Chongqing Public Health Medical Center, Chongqing, China*

**Background:** Pneumocystis pneumonia is a common opportunistic infection in HIV/AIDS patients, and is a leading cause of death in this population. Early selection of effective treatment is therefore critical to reduce mortality. We conducted a clinical trial to compare the effectiveness and safety of three different antifungal treatment regimens in HIV-infected patients with moderate to severe PCP.
**Methods:** Our study was a multicenter, observational prospective clinical trial. We recruited 320 HIV-positive patients with moderate to severe PCP, and stratified these subjects into trimethoprim/sulfamethoxazole monotherapy group, trimethoprim/sulfamethoxazole plus clindamycin group, and trimethoprim/sulfamethoxazole plus caspofungin group. Patients were invited to participate in 12-weeks of follow-up. Outcomes included the difference in overall mortality in the three groups at week 4 and week 12, the proportion of overall positive response to treatment of moderate to severe PCP in each group at week 4 and week 12, the difference in treatment duration among the three groups, and the difference in the proportion of adverse events among the three groups during the study period.
**Results:** In total, we enrolled 320 patients in this study. Baseline clinical and laboratory characteristics of patients were comparable among the three groups. Our data showed that mortality rates in moderate to severe PCP patients with HIV were not significantly different among the three groups of patients in our study, both at week 4 and at week 12. Our results showed that the median duration of treatment was 21 days in each of the 3 groups. The overall positive response rate to treatment in the three groups at week 4 was 22.76%, 35.56% and 37.38%, respectively. There were statistically significant differences at week 4 in the overall positive response rate to treatment in each group. We did not observe any significant difference in the overall positive response rate to treatment at week 12. Meanwhile, there were no significant differences in adverse events among the three groups of patients with moderate to severe PCP.
**Conclusion:** Our results indicate that trimethoprim/sulfamethoxazole plus clindamycin or caspofungin may be more suitable for the management of HIV-positive patients with moderate to severe PCP compared with trimethoprim/sulfamethoxazole monotherapy.

## 670 HIV AND SARS-CoV-2 INFECTION AMONG POSTPARTUM KENYAN WOMEN AND THEIR INFANTS

New Investigator Scholar

**Emily R. Begnel**[1], Bhavna Chohan[1], Ednah Ojee[2], Judith A. Onyango[2], Prestone Owiti[2], LaRinda A. Holland[3], Barbra A. Richardson[1], Adam K. Khan[3], Rabia Maqsood[3], Efrem S. Lim[3], Dara A. Lehman[4], Jennifer Slyker[1], John Kinuthia[5], Dalton C. Wamalwa[2], Soren Gantt[6]
*[1]University of Washington, Seattle, WA, USA, [2]University of Nairobi, Nairobi, Kenya, [3]Arizona State University, Tempe, AZ, USA, [4]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [5]Kenyatta National Hospital, Nairobi, Kenya, [6]Centre de Recherche du CHUM, Montreal, Canada*

**Background:** People living with HIV may have increased risk of SARS-CoV-2 infection and severe COVID-19. However, few studies have examined the risk and outcomes of SARS-CoV-2 infection specific to postpartum women living with HIV and their HIV-exposed, uninfected (HEU) infants. To address this gap, we compared incidence, risk factors, and symptomatology of SARS-CoV-2 infection among mother-infant pairs living with and without HIV.
**Methods:** We conducted a nested study of healthy mothers and infants enrolled in a Nairobi, Kenya-based prospective cohort study. Women living with HIV were enrolled in the parent cohort only if on antiretroviral therapy (ART) for ≥6 months. SARS-CoV-2 serology was performed on plasma collected between 1 May-31 December 2020 to assess incidence of infection and duration of antibody detection. SARS-CoV-2 RNA PCR and sequencing was also conducted on stool from seropositive participants. Sociodemographic and clinical data were used to evaluate risk factors for SARS-CoV-2 with Cox regression and to assess symptomatic COVID-19 with generalized estimating equations.
**Results:** Among 104 mothers (51 living with HIV, 53 HIV-uninfected) and 89 infants (41 HEU, 48 HIV-unexposed), SARS-CoV-2 seropositivity was 38% and 17%, respectively. Incidence of infection did not differ significantly between women living with HIV and HIV-uninfected women (Hazard Ratio [HR]=1.51, 95% CI:0.78-2.94) or HEU and HIV-unexposed infants (HR=1.48, 95% CI:0.54-4.09). Maternal SARS-CoV-2 substantially increased risk of infant infection, regardless of HIV exposure (HR=10.3, 95% CI:2.89-36.8). However, no other factors-including CD4 count and years on ART among women living with HIV-were associated with infection. Antibody levels waned below detection in ~30% of mothers and infants after a mean of 6 and 5 months, respectively. Among seropositive participants, SARS-CoV-2 RNA was detected among 5 of 27 mothers (19%) and one of 13 infants (8%) with samples. Sequences recovered from 2 samples were related to circulating variants in Kenya in 2020. One-fifth of participants had mild to moderate symptoms, but there were no cases of severe COVID-19 or death.
**Conclusion:** Our findings show there was a high risk of SARS-CoV-2 infection among postpartum Kenyan women and their infants in 2020, though this

risk was not substantially increased for women with well-managed HIV and most cases were asymptomatic. Rapidly waning antibody responses suggest continued preventive measures are needed until vaccination is widely available.

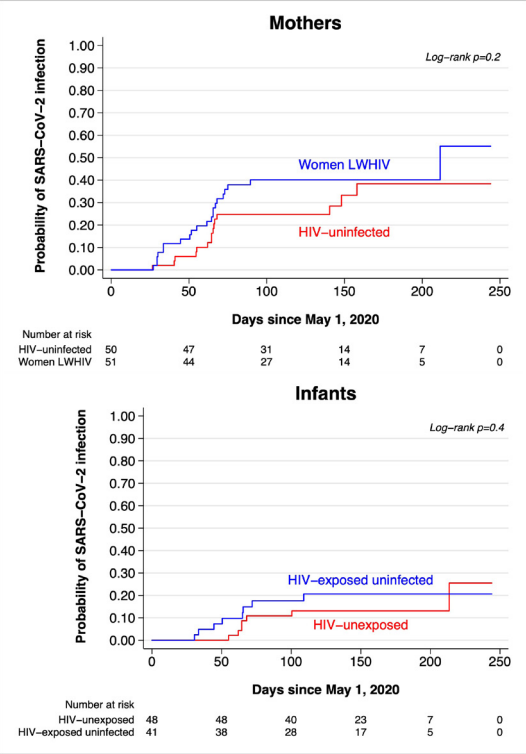



**Figure 1. Kaplan-Meier hazard functions for estimated date of SARS-CoV-2 infection among postpartum Kenyan and their infants, by maternal HIV status or infant HIV exposure.**

## 671 ADVERSE PREGNANCY OUTCOMES ASSOCIATED WITH COVID-19 INFECTION IN WESTERN KENYA

**Victor Akelo**[1], Gregory Ouma[2], Joyce Were[2], Sammy Khagayi[2], Dickson Gethi[2], Richard Omore[2], Feiko ter Kuile[3], Marc Bulterys[4], Dickens Onyango[5], Beth A.T. Barr[1]

*[1]US Centers for Disease Control and Prevention, Kisumu, Kenya, [2]Kenya Medical Research Institute, Kisumu, Kenya, [3]Liverpool School of Tropical Medicine, Liverpool, UK, [4]US Centers for Disease Control and Prevention, Nairobi, Kenya, [5]Kisumu County Health Department, Kisumu, Kenya*

**Background:** The COVID-19 pandemic has caused over 240 million infections and 5 million deaths. Little is known about the impact of COVID-19 on pregnancy outcomes in Sub-Saharan Africa. We followed a cohort of COVID-infected and uninfected pregnant women in Kenya until six weeks postpartum to assess the burden of COVID-19 and its association with poor maternal and neonatal outcomes.

**Methods:** We conducted repeat SARS-CoV-2 testing using polymerase chain reaction (PCR) on pregnant women enrolled in an antenatal COVID-19 cohort study (AnCOV). Those infected were managed according to Kenya Ministry of Health COVID-19 clinical guidelines. Adverse pregnancies outcomes were compared among SARS-CoV-2 infected and uninfected women using multivariate log-binomial generalized linear models.

**Results:** Between August 2020 and August 2021, 1688 pregnant women were enrolled; 998 completed pregnancy follow-up. Of those, 259 (26.0%) had adverse outcomes, and 169 (22%) tested positive for SARS-CoV-2, of whom 93 (55%) were symptomatic. The most prevalent symptoms included cough (76.1%), headache (47.9%), anorexia (41%), anosmia (35.0%), fatigue (30.8%), joint pains (29.1%), fever (28.2%), runny nose (23.1%), chills (19.7%) and myalgia (12.8%). Fourteen COVID-19 pregnant women required hospitalization; none were admitted in ICU. Very low birthweight (<1500g) (adjusted relative risk (aRR) 4.78, 95% CI 1.11-20.49), very preterm birth (<34 weeks) (aRR=2.57, 1.34-4.90) and preterm birth (<37 weeks) (aRR=1.54, 1.03-2.29) were more common among women with COVID-19. There were no significant associations between COVID-19 in pregnancy and hypertensive disorders of pregnancy, preeclampsia, stillbirths and perinatal deaths.

**Conclusion:** SARS-CoV-2 infection increases the risk of very low birth weights and very preterm births in western Kenya.

**Table 1: Pregnancy outcomes comparing COVID-19 infected and non-COVID-19 infected pregnant women enrolled in an antenatal, intrapartum and post-partum COVID-19 (AnCoV) prospective study in western Kenya, 2020-2021**

| Outcome | Total | Unadjusted Risk Ratio | | Adjusted Risk Ratio | |
|---|---|---|---|---|---|
| *Maternal Outcomes*[1] | n (%) | Unadjusted RR (95% CI) | *p-value* | Adjusted RR[2] | *p-value* |
| Hypertensive disorders of pregnancy | 22 (2.0) | 1.15 (0.26, 5.05) | *0.857* | 1.17 (0.27, 5.17) | *0.832* |
| Preeclampsia | 3 (0.3) | 6.88 (0.43, 109.18) | *0.172* | 6.99 (0.42, 116.88) | *0.176* |
| Preeclampsia or Eclampsia | 3 (0.3) | 6.88 (0.43, 109.18) | *0.172* | 6.99 (0.42, 116.88) | *0.176* |
| ***Fetus/Infant Outcomes*** | | | | | |
| Stillbirth | 48 (4.8) | 0.40 (0.05, 3.0) | *0.368* | 0.40 (0.05, 2.99) | *0.372* |
| Perinatal death | 9 (0.9) | 0.27 (0.04, 2.00) | *0.197* | 0.28 (0.04, 2.08) | *0.215* |
| Very low birthweight (<1500g) | 8 (1.0) | **4.99 (1.13, 22.00)** | ***0.034*** | **4.78 (1.11, 20.49)** | ***0.035*** |
| Low birthweight (<2500g) | 63 (6.0) | 1.63 (0.87, 3.05) | *0.129* | 1.61 (0.86, 3.01) | *0.138* |
| Very preterm birth (<34 weeks) | 88 (8.0) | 1.23 (0.69, 2.20) | *0.488* | 1.32 (0.74, 2.37) | *0.345* |
| Preterm birth (<37 weeks) | 222 (22.0) | 1.02 (0.71, 1.46) | *0.924* | 1.07 (0.75, 1.53) | *0.714* |
| Very preterm birth (<34 weeks) - COVID+ onset <34w | 83 (8.0) | **2.44 (1.26, 4.69)** | ***0.008*** | **2.57 (1.34, 4.90)** | ***0.004*** |
| Preterm birth (<37 weeks) - COVID+ onset <37w | 212 (21.0) | 1.49 (0.99, 2.24) | *0.053* | **1.54 (1.03, 2.29)** | ***0.036*** |

[1]*Adjusted for age (categorical; "underage 20" and "age 35 and older" as confounders)*
[2]*No maternal deaths were documented during the course of the study*

## 672 SARS-CoV-2 INFECTION AND PREGNANCY IN AFRICA: A 6-COUNTRY RETROSPECTIVE COHORT STUDY

**Jean Nachega**[1], Nadia Sam-Agudu[2], Rhoderick Machekano[3], Philip J. Rosenthal[4], Onesmus Gachuno[5], John Kinuthia[5], Nancy Mwongeli6, Philippa Musoke[7], Musa Sekikubo[8], Jean-Jacques Muyembe-Tamfum[9], Denis Mukwege[10], John W. Mellors[11], Lynne Mofenson[12], Eduard J. Langenegger[13]

*[1]University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA, [2]Institute of Human Virology and Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA, [3]Stellenbosch University, Cape Town, South Africa, [4]University of California San Francisco, San Francisco, CA, USA, [5]University of Nairobi, Nairobi, Kenya, [6]Kenyatta National Hospital, Nairobi, Kenya, [7]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [8]Makerere University College of Health Sciences, Kampala, Uganda, [9]Institut National de la Recherche Bio-Medicale, Kinshasa, Congo, The Democratic Republic Of The, [10]Panzi Referral Hospital, Bukavu, Congo, The Democratic Republic Of The, [11]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [12]Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, [13]Stellenbosch University, Tygerberg, South Africa*

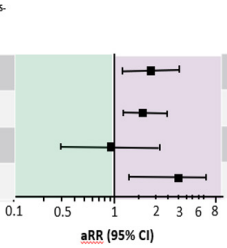
**Background:** Limited data are available on pregnancy and COVID-19 in sub-Saharan Africa (SSA).

**Methods:** We conducted a retrospective cohort study of women ≥18 years old hospitalized at 23 health facilities in six SSA countries between March 1, 2020, and March 31, 2021. We assessed the impact of pregnancy on SARS-CoV-2 infection, and of SARS-CoV-2 on pregnant women, through comparisons of clinical outcomes among: 1) pregnant and non-pregnant women hospitalized with RT-PCR-confirmed SARS-CoV-2 infection, and 2) pregnant women confirmed to be positive or negative for SARS-CoV-2 infection by RT-PCR. The primary outcome for both analyses was intensive care unit (ICU) admission. Secondary outcomes included need for oxygen supplementation or mechanical ventilation, pregnancy outcomes, and maternal or neonatal mortality. We performed negative log-binomial regression models to estimate the impact of pregnancy on SARS-CoV-2 among all women in the cohort, and the impact of SARS-CoV-2 on pregnancy outcomes. Factors associated with mortality were evaluated using competing-risk regression based on Fine and Gray's proportional hazards model.

**Results:** We analyzed data on 1,315 hospitalized women: 510 pregnant women with SARS-CoV-2 infection; 403 non-pregnant women with SARS-CoV-2 infection, and 402 pregnant women without SARS-CoV-2 infection. Among those with SARS-CoV-2 infection, pregnancy was associated with increased risk of ICU admission (adjusted rate ratio [aRR]= 1.86, 95% CI: 1.07 – 3.22, p=0.003) and oxygen supplementation (aRR= 1.48, 95% CI: 1.06 – 2.08, p=0.001). Among pregnant women, those with SARS-CoV-2 infection had increased risk of ICU admission (aRR = 2.0, 95% CI: 1.20 – 3.35, p=0.008), oxygen supplementation (aRR = 1.57, 95% CI: 1.17 – 2.11, p=0.002) and maternal mortality (aRR=3.08, 95% CI: 1.21 – 7.85, p=0.018) (Figure). Comparing SARS-CoV-2-infected vs. uninfected pregnant women, infected women were more likely to deliver by Caesarean section (59.3% vs 37.9%, RR = 1.56, 95% CI: 1.29 – 1.89, p<0.001); however, proportions of pre-term infants (32.4% vs. 31.1%, respectively, p = 0.870), infants with low birth weight (33.8% vs. 30.9%, respectively, p=0.711) and neonatal deaths [8/209 (3.8%) vs. 8/306 (2.6%) (RR=1.46, 95% CI: 0.56 – 3.84, p=0.436, respectively)] were similar.

**Conclusion:** Among hospitalized pregnant women, SARS-CoV-2 infection increased morbidity and mortality. These data support international recommendations to prioritize COVID-19 vaccination among pregnant women.

| Outcomes | Pregnant SARS-CoV-2-Infected n (%) | Pregnant SARS-CoV-2-Uninfected n(%) | aRR (95% CI) | *P*-Value |
|---|---|---|---|---|
| ICU Admission | 95 (18.6) | 23 (5.7) | 2.00 (1.20 – 3.35) | 0.008 |
| Oxygen Therapy | 164 (32.2) | 66 (16.4) | 1.57 (1.17 – 2.11) | 0.002 |
| Mechanical Ventilation | 20 (4.0) | 12 (3.0) | 0.90 (0.38 – 2.15) | 0.81 |
| Death | 51 (10.1) | 6 (1.5) | 3.08(1.21 – 7.85) | 0.001 |

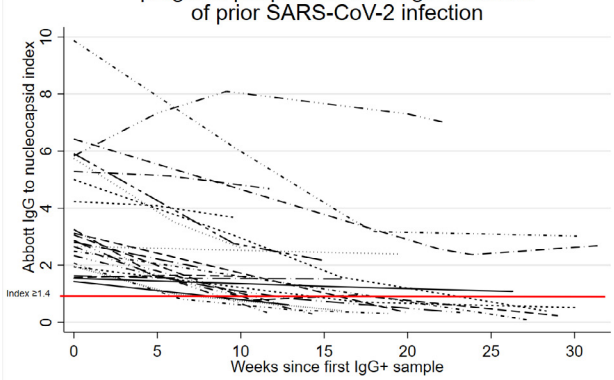



## 673 LONGITUDINAL SARS-CoV-2 ANTIBODY RESPONSE IN PREGNANCY AND TRANSPLACENTAL TRANSFER

**Sylvia LaCourse**[1], Morgan Aurelio[1], Jaclyn Escudero[1], Sascha R. Ellington[2], Lauren B. Zapata[2], Margaret C. Snead[2], Viral Upadhyay[2], Krissy Yamamoto[1], Carol Salerno[1], Alex Greninger[1], Alisa Kachikis[1], Janet A. Englund[1], Alison L. Drake[1]
*[1]University of Washington, Seattle, WA, USA, [2]Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** Longitudinal assessment of SARS-CoV-2 antibody (Ab) response during pregnancy after infection and transplacental transfer may inform durability of maternally derived Ab for mothers and infants.
**Methods:** Between October 2020-September 2021, pregnant people testing SARS-CoV-2 IgG positive by Abbott Architect chemiluminescent immunoassay (CMIA) for anti-nucleocapsid (N) antibody (semi-quantitative index ≥1.4 considered IgG+) during pregnancy or delivery in a seroprevalence study, or identified with RT-PCR+ results via medical records, were invited to enroll in a longitudinal evaluation of maternal Ab responses and transplacental transfer. Maternal blood collected at 1, 2, 3, and 6 months after enrollment and maternal and cord blood collected at delivery were tested with the same assay.
**Results:** Among 40 participants testing IgG+ for anti-N, 31 (78%) had a prior RT-PCR+ result. Median age was 32 years (IQR 29-35); 27 (68%) enrolled during pregnancy at median 18 weeks gestation (IQR 13-33), while 13 (33%) enrolled at delivery or early postpartum. Median Abbott index was 3.06 (IQR 1.96-5.74) at first IgG+ result obtained at a median of 9 weeks (IQR 4-16) after RT-PCR+ result, for those with a known RT-PCR. Among 23 participants with ≥2 samples, 50% had IgG results below positivity threshold at median 17 weeks (IQR 12-28) after first IgG+ result (Figure). Seventeen mother-infant pairs had delivery samples collected at median 66 days (IQR 60-71 days) from maternal RT-PCR+ result. Six (35%) maternal samples remained IgG+ (median Abbott index 2.97 [IQR 2.35-7.01]) at delivery (gestational age 30–40 weeks) with all 6 paired cord sera testing IgG+ (median Abbott index 4.30 [IQR 2.93-7.22]). Median placental transfer ratio of maternally derived IgG Abs based on a positive Abbott index was 1.13 (95%CI 0.98-1.30) among mothers with samples remaining IgG+ at delivery.
**Conclusion:** Within 4 months after first IgG+ result primarily in second trimester, about half of pregnant persons had SARS-CoV-2 IgG anti-N Ab levels below the Abbott CMIA positive threshold. Among evaluable mother-infant pairs, two-thirds of mothers no longer tested anti-N IgG+ at delivery. Transplacental transfer of maternal antibodies was confirmed in all infants born to mothers with samples remaining IgG+ at delivery. Durability of maternal SARS-CoV-2 Ab response and transplacental transfer following infection has implications for maternal and neonatal susceptibility to SARS-CoV-2 infection.

Figure: Abbott IgG to nucleocapsid index among pregnant people with serologic evidence of prior SARS-CoV-2 infection

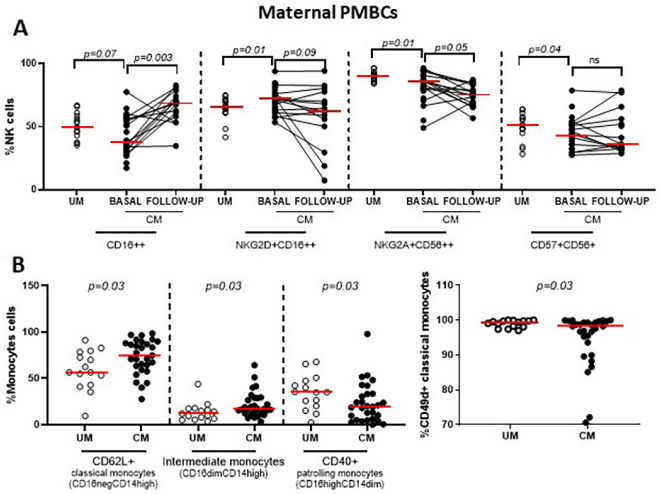


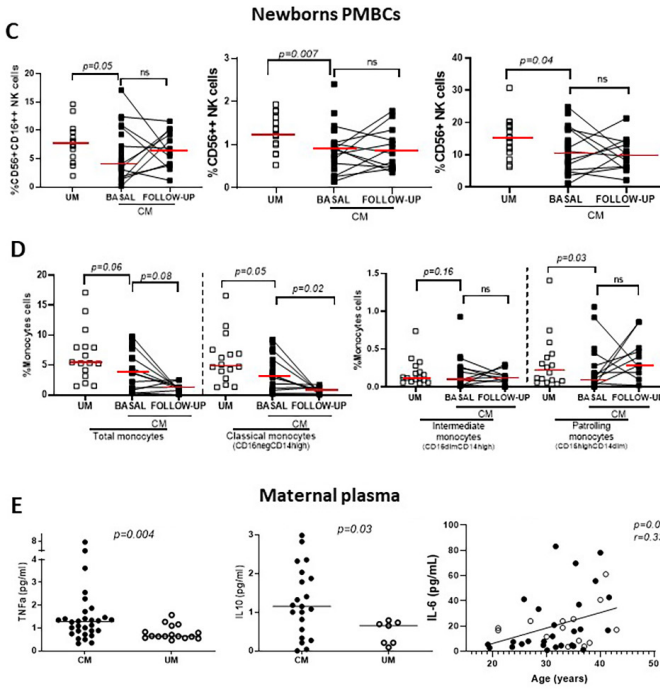

## 674 IMMUNE SYSTEM PROFILE AND CYTOKINE LEVELS OF SARS-CoV-2 IN PREGNANCY AND NEWBORNS

New Investigator Scholar

**Elena Vázquez Alejo**[1], Laura Tarancon-Diez[1], Itziar Carrasco[1], Sara Vigil-Vazquez[1], Mar Muñoz-Chapuli[1], Elena Rincón López[1], Jesús Saavedra-Lozano[1], Mar Santos Sebastián[1], Juan Antonio De León Luis[1], Manuel Sánchez-Luna[1], María Luisa Navarro[1], Maria Ángeles Muñoz-Fernández[1]
*[1]Hospital General Universitario Gregorio Marañón, Madrid, Spain*

**Background:** Knowledge about SARS-CoV2 infection in pregnancy and exposed newborns is deficient. We performed a longitudinal analysis of innate immune system status and determined soluble cytokines of women infected with SARS-CoV2 during pregnancy and their newborns
**Methods:** Women with confirmed SARS-CoV2 infection (RT-PCR+ or SARS-CoV2 anti-IgM/IgG+) (COVID MOTHER group, CM n=29, median age of 31 years) and their SARS-CoV2 exposed uninfected newborns were recruited from Hospital Gregorio Marañón, Spain. Peripheral blood mononuclear cells (PBMCs), cord cells and plasma were collected at birth and 6 months later (n=15). The immunophenotyping of innate components (natural killer cells [NK] and monocytes) was studied on cryopreserved PBMCs and cord cells by multiparametric flow cytometry. Up to 4 soluble pro/anti-inflammatory cytokines were assessed in plasma and cord plasma by ELISA assay. CM was compared to a healthy non-SARS-CoV2 infected mothers' group matched by age (SARS-CoV2 PCR- and SARS-CoV2 anti-IgM/IgG-)(Uninfected Mothers, UM n=16) and their newborns (n=16)
**Results:** On NK cell assays, CM show at baseline lower percentage of CD16++ subset, higher NKG2D and lower NKG2A expression on CD16++ and CD56++ subsets and reduced CD57 expression compared to UM; proportion of CD16++ subset and percentage of NKG2D reverted after 6 months(A). Regarding monocytes, CM show increased levels of CD62L and decreased CD49d expression on classical subset, elevated intermediate monocytes proportion and decreased CD40 expression on patrolling subset(B). No differences were found 6 months later. No newborn was infected by SARS-CoV2 and the phenotype analyzed on cord cells shows lower frequency of NK subsets compared with unexposed children and increased CD16++ subset after 6 months(C). In monocytes distribution, exposed children present lower frequency of total monocytes and its subsets than unexposed. Classical monocytes show significant changes at follow-up time-point(D). Increased TNFα and IL10 levels were found on CM compared to UM. Strong and direct correlations were observed between the age and IL6(E). No differences were observed in soluble cytokine levels comparing both groups of newborns
**Conclusion:** SARS-CoV2 infection during pregnancy shows differences in activation, maturation and endothelial markers on innate immune system that could lead newborns clinical implications at birth. However, altered cell proportions and phenotypes found at SARS-CoV2 at birth time and on their exposed newborns is later reverted.

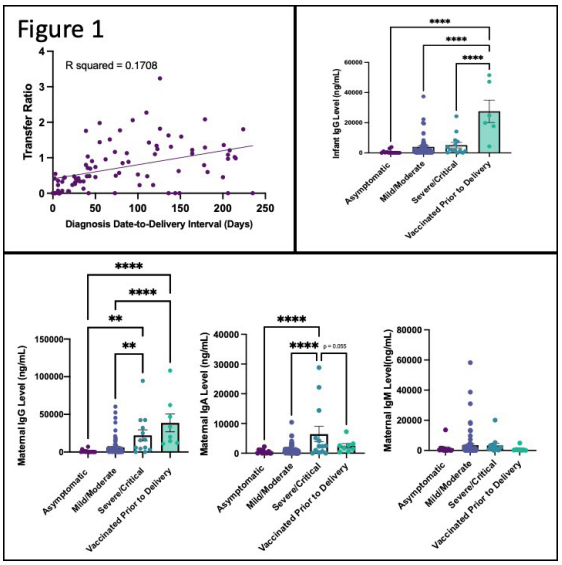





## 675 NEUTRALIZING ANTIBODY RESPONSE AND TRANSPLACENTAL TRANSFER IN COVID-19 IN PREGNANCY

**Mary C. Cambou**[1], Christine M. Liu[1], Thalia Mok[1], Viviana Fajardo Martinez[1], Sophia G. Paiola[1], Francisco J. Ibarrondo[1], Tara Kerin[1], Nicole Tobin[1], Gustavo Garcia[1], Debika Bhattacharya[1], Grace M. Aldrovandi[1], Vaithilingaraja Arumugaswami[1], Rashmi Rao1, Otto Yang[1], Karin Nielsen-Saines[1]
*[1]University of California Los Angeles, Los Angeles, CA, USA*

**Background:** There are limited data on how COVID-19 disease severity and vaccination throughout different trimesters in pregnancy impact maternal neutralizing antibody responses and transplacental transfer to the neonate at birth. Further characterization of the antibody response of in utero SARS-CoV-2 may inform vaccination schedules in pregnancy in order to optimize maternal and neonatal protection.
**Methods:** The COVID-19 Outcomes in Mother-Infant Pairs (COMP) study is a longitudinal cohort of mother-infant dyads diagnosed with PCR-confirmed SARS-CoV-2 at any point during pregnancy. Maternal and cord sera from delivery, as well as infant sera collected at 24 hours of life, were analyzed by enzyme-linked immunosorbent assay (ELISA) for IgA, IgG, and IgM targeting receptor binding domain (RBD) of the SARS-CoV-2 spike protein. Neutralizing antibody (NAb) activity against the original L strain was evaluated in a subset of unvaccinated mother-infant dyads with evidence of IgG transfer or history of severe/critical COVID-19 in pregnancy.
**Results:** Among 115 pregnant women, the NIH COVID-19 severity of illness categories were: 12% asymptomatic, 70% mild/moderate, 11% severe/critical disease, and 7% vaccinated prior to delivery following recovery. Fifty percent of the cohort was diagnosed in the 3rd trimester, and the median diagnosis date to delivery was 61.5 days (IQR 27.75 – 122.25). The majority (74%) of the cohort produced all three anti-SARS-CoV-2 isotypes, although 5% had no detectable antibody class. Transplacental transfer ratios increased with increasing duration between onset of infection and delivery (Figure 1, r2=0.17). Infant IgG levels (ng/mL) were the highest among neonates born to vaccinated mothers (Figure 1), and maternal IgG levels increased with disease severity, although vaccination elicited a comparable maternal antibody response to severe/critical disease (Figure 1). Among 50 maternal specimens, 80% demonstrated in vitro neutralization activity, and 52% of 33 neonatal specimens had NAb.
**Conclusion:** While transplacental transfer of IgG was high with natural infection and correlates with increasing duration between onset of infection and delivery, only half of analyzed neonatal specimens demonstrated in vitro neutralization activity. Further research is needed to characterize the functionality and kinetics of both maternal and neonatal antibody responses elicited by in utero SARS-CoV-2 natural infection compared with COVID-19 vaccination.




## 676 IMPAACT 2032: REMDESIVIR PK & SAFETY IN PREGNANT AND NON-PREGNANT WOMEN WITH COVID-19

**Kristina M. Brooks**[1], Kristin Baltrusaitis[2], Jeremiah Momper[3], Elizabeth Greene[4], Frederic Bone[5], Kira Bacon[5], Rita Humeniuk[6], Dwight E. Yin[7], Nahida Chakhtoura[8], Alice M. Stek[9], Edmund Capparelli[3], Mark Mirochnick[10], Diana F. Clarke[11], Brookie M. Best[3]
*[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, University of California San Diego, La Jolla, CA, USA, [4]FHI 360, Durham, NC, USA, [5]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [6]Gilead Sciences, Inc, Foster City, CA, USA, [7]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [8]National Institute of Child Health and Human Development, Bethesda, MD, USA, [9]University of Southern California, Los Angeles, CA, USA, [10]Boston University, Boston, MA, USA, [11]Boston Medical Center, Boston, MA, USA*

**Background:** Pregnant people with COVID-19 are at higher risk of severe disease and adverse pregnancy outcomes. Remdesivir (RDV), an antiviral medication that is US FDA-approved for severe COVID-19, has limited data during pregnancy. Here we report preliminary pharmacokinetic (PK) and safety data for RDV in pregnant and non-pregnant women with COVID-19.
**Methods:** IMPAACT 2032 is an ongoing phase IV prospective, open-label, non-randomized opportunistic study of pregnant and non-pregnant women prescribed RDV for COVID-19 treatment as part of clinical care. RDV was administered intravenously at a 200 mg dose on Day 1 followed by 100 mg once-daily through 5 or 10 days of treatment. Enrollment occurred prior to the 4th infusion. Repeat PK sampling was performed through 23 hours post-infusion on infusion day 3, 4 or 5. Baseline demographic and clinical data were recorded from 48 hours pre-1st infusion, and safety data were recorded from 1st infusion through 4 weeks post-last infusion and at labor/delivery for pregnant women. Adverse events (AEs) were graded according to the DAIDS AE Grading Table v2.1. RDV and its plasma metabolites (GS-704277 and GS-441524) were quantified using validated LC/MS methods. PK parameters were estimated using noncompartmental methods (Phoenix WinNonlin®).
**Results:** This preliminary analysis included 18 women: 10 pregnant (median (range) gestational age 28 (22-32) weeks) and 8 non-pregnant (Table). One pregnant woman withdrew consent before completing RDV treatment; 3 discontinued RDV early (2 pregnant women due to hospital discharge; 1 non-pregnant woman due to grade 2 bradycardia related to RDV). Thirteen women completed 5 days and 1 completed 10 days of treatment. Plasma RDV and metabolite exposures were comparable between 8 pregnant and 6 non-pregnant PK-evaluable women (Table). Among safety-evaluable women (n=18), 8 pregnant and 4 non-pregnant women had ≥1 grade 3/4 AE; 1 grade 3 AE was related to RDV in a non-pregnant woman (estimated glomerular filtration rate (eGFR) 30-<60 mL/min). Of 6 women with delivery data available, there were 2 preterm births (<37 weeks) and 1 intrauterine fetal demise (26 weeks), which was unrelated to RDV.
**Conclusion:** Preliminary estimates of RDV, GS-704277 and GS-441524 exposures were generally comparable between pregnant and non-pregnant

women, but no formal statistical comparisons were made. PK (including intracellular) and safety investigations in additional women are ongoing.

**Table. IMPAACT 2032 Demographics & PK Results**

| Measure | Pregnant Women | Non-Pregnant Women |
|---|---|---|
| **Demographics** | **n=10** | **n=8** |
| Age (yr), median (range) | 32 (23-45) | 42 (28-45) |
| Weight (kg), median (range) | 79.1 (68.0-171.3) | 119.5 (64.7-161.6) |
| Race & Ethnicity, n(%) | | |
| White & not Hispanic/Latina | 2 (20%) | 2 (25%) |
| Black & not Hispanic/Latina | 3 (30%) | 5 (62.5%) |
| White & Hispanic/Latina | 3 (30%) | 1 (12.5%) |
| Unknown & Hispanic/Latina | 2 (20%) | 0 (0%) |
| eGFR (mL/min/1.73 $m^2$), median (range) | 121 (60-157) | 75 (41-137) |
| **PK Parameters, geometric mean (CV%)** | **n=8** | **n=6** |
| RDV $AUC_{0\text{-}24h}$ (ng*h/mL)[a] | 776 (87.5%) | 1023 (32.7%) |
| RDV $t_{1/2}$ (h)[a] | 0.98 (42.3%) | 1.34 (55.3%) |
| GS-704277 $AUC_{0\text{-}24h}$ (ng*h/mL) | 387 (26.5%) | 401 (29.7%) |
| GS-441524 $AUC_{0\text{-}24h}$ (ng*h/mL) | 1689 (30.5%) | 2118 (42.8%) |
| GS-441524 $C_{24h}$ (ng/mL) | 47.9 (38.7%) | 54.4 (57.8%) |

Key: $AUC_{0\text{-}24h}$ = area under the concentration-time curve from time 0 through 24 hours; $C_{24h}$: concentration at 24 hours post-dose; eGFR = estimated glomerular filtration rate; $t_{1/2}$ = half-life.
[a]RDV $AUC_{0\text{-}24h}$ and $t_{1/2}$ in 6 pregnant and 5 non-pregnant women

## 677 NEURAL TUBE DEFECTS AND PRENATAL EXPOSURE TO DOLUTEGRAVIR: UNITED STATES, 2008-2019

Late Breaking

**Athena Kourtis**[1], Weiming Zhu[1], Margaret Lampe[1], Ya-Lin A. Huang[1], Karen W. Hoover[1]

*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** A study from Botswana identified an elevated risk of neural tube defects (NTD) in infants of mothers with HIV treated with dolutegravir (DTG) around the time of conception. Comprehensive data from the United States, a setting with folic acid fortification of food, have not been reported.

**Methods:** We analyzed the IBM MarketScan Commercial Claims and Encounters Database and the Centers for Medicare and Medicaid Services data from 2008-2019. We identified pregnancies with enrollment during their whole duration among women aged 15-49y; for this cohort, we determined presence of HIV diagnosis and antiretroviral (ARV) prescriptions by type of ARV. We developed an algorithm to estimate time of conception, identify pregnancy outcomes, and match infants with NTD diagnoses to their mothers. We estimated incidence of NTD by type of ARV (DTG vs any other ARV) periconceptionally and during first trimester (8 weeks before conception -13 weeks gestation). As severe congenital defects can lead to prenatal death, we also estimated the incidence of stillbirths and spontaneous and induced abortions.

**Results:** We identified 17,544,269 pregnancies (weighted) in MarketScan and 18,904,008 in Medicaid over the study period (Table); of these, 22,129 (0.1%) and 84,388 (0.4%) had a HIV diagnosis, respectively. Among these, 509 pregnancies in commercially insured women and 2,331 in Medicaid had early exposure to DTG. No NTDs were identified in commercially insured women, and one case (spinal bifida) was identified in Medicaid, with an incidence of 0.66 per 1,000 livebirths. The corresponding rates of NTD in infants of women without HIV were 0.76 per 1,000 in commercially insured women, and 0.91 per 1,000 in Medicaid. Similarly low rates of NTD were observed among women with HIV and early pregnancy exposure to other ARV (Table). Women with HIV had higher rates of stillbirths and pregnancy losses compared with women without HIV.

**Conclusion:** We studied the largest U.S. cohort of periconceptional/early pregnancy DTG exposures and provide compelling evidence on the safety of DTG during conception and early pregnancy. The results are reassuring, as they do not demonstrate an increased risk of NTD in the U.S., and support the current U.S. federal perinatal guidelines. In the absence of nationwide surveillance, the pregnancy algorithm we developed can be used with administrative databases to study correlates of rare outcomes such as NTD and to monitor adverse pregnancy outcomes of ARV use in U.S. women.

**Table. Risk ratios (95% confidence intervals) of neural tube defects (NTD) and adverse outcomes in pregnancies with exposure to dolutegravir (DTG) or other antiretroviral (ARV) medications periconceptionally and during the first trimester, compared to women without HIV, MarketScan commercial and Medicaid databases 2008-2019**

| | Women without HIV | Women with HIV, DTG in early pregnancy | | Women with HIV, Other ARV in early pregnancy | |
|---|---|---|---|---|---|
| | Number (Rate per 1,000 pregnancies) | Number (Rate per 1,000 pregnancies) | Risk Ratio (95% Confidence Interval) | Number (Rate per 1,000 pregnancies) | Risk Ratio (95% Confidence Interval) |
| **MarketScan (Weighted)** | | | | | |
| **Pregnancies (N)** | 17,522,140 | 509 | | 6,892 | |
| **Live births** | 12,988,678 (741.27) | 316 (620.48) | 0.84 (0.78–0.90)* | 4,426 (642.19) | 0.87 (0.85–0.88)* |
| **NTD**** | 9,901 (0.76) | 0 (0.00) | NA | 4 (0.90) | 1.19 (0.45–3.16) |
| **Stillbirths** | 108,164 (6.17) | 8 (15.71) | 2.55 (1.28–5.06)* | 83 (12.04) | 1.95 (1.58–2.44)* |
| **Pregnancy losses§** | 4,304,478 (245.66) | 185 (363.26) | 1.48 (1.32–1.66)* | 2,304 (334.30) | 1.36 (1.32–1.41)* |
| **Medicaid** | | | | | |
| **Pregnancies (N)** | 18,904,008 | 2,331 | | 18,437 | |
| **Live births** | 15,515,806 (820.77) | 1,515 (649.94) | 0.79 (0.77–0.82)* | 13,182 (714.98) | 0.87 (0.86–0.88)* |
| **NTD**** | 14,152 (0.91) | 1 (0.66) | 0.72 (0.10–5.13) | 9 (0.68) | 0.75 (0.39–1.44) |
| **Stillbirths** | 104,465 (5.53) | 12 (5.15) | 0.93 (0.53–1.64) | 130 (7.05) | 1.28 (1.08–1.51)* |
| **Pregnancy losses§** | 3,205,797 (169.58) | 795 (341.06) | 2.01 (1.90–2.13)* | 4,976 (269.89) | 1.59 (1.55–1.63)* |

* P < 0.05; **per 1,000 livebirths; §Pregnancy losses included spontaneous and induced abortions.

## 678 BIRTH OUTCOMES FOLLOWING PRENATAL EXPOSURE TO DOLUTEGRAVIR: THE DOLOMITE-EPPICC STUDY

**Claire Thorne**[1], Karoline Aebi-Popp[2], Luminita Ene[3], Marco Floridia[4], Anna Maria Gamell[5], Marta Illan[6], Helen Peters[1], Anna Samarina[7], Leigh Ragone[8], Carlo Giaquinto[9], Vani Vannappagari[8]

*[1]University College London, London, UK, [2]University Hospital Bern, Bern, Switzerland, [3]Victor Babes Hospital, Bucharest, Romania, [4]Istituto Superiore di Sanità, Rome, Italy, [5]Hospital Sant Joan de Déu Barcelona, Esplugues, Spain, [6]Hospital Universitario Clí¬nico San Carlos, Madrid, Spain, [7]St Petersburg City Centre for AIDS and Infectious Diseases, St Petersburg, Russian Federation, [8]ViiV Healthcare, Research Triangle Park, NC, USA, [9]University of Padova, Padova, Italy*

**Background:** Dolutegravir (DTG) is recommended and widely used during pregnancy for maternal viral suppression and preventing perinatal transmission of HIV. Our objective is to assess pregnancy and neonatal outcomes including birth defects following prenatal DTG use using real-world European data.

**Methods:** Dolomite-EPPICC is a multi-cohort European observational study of DTG use in pregnant women living with HIV and their infants. An analysis of prospectively collected data on all pregnancies with any prenatal DTG exposure and with birth outcomes was conducted among participating cohorts from Italy, Romania, the Russian Federation, Spain, Switzerland and UK/Ireland. Periconception exposure was defined as being within the first 6 weeks of gestation.

**Results:** Overall, 550 pregnancies (540 singleton, 10 twin pregnancies) from 7 cohorts were included in the analysis resulting in 508 liveborn infants (491 singletons and 17 twins). Overall, 72.1% (365/506) pregnancies were in parous women. A total of 27 pregnancies ended in spontaneous abortion, 18 pregnancies were terminated and five ended in still birth. One termination was for neuronal migration disorder and severe microcephaly, with periconception DTG exposure. All stillbirths were exposed to periconception DTG, none with birth defects. Among the 508 liveborn infants, earliest DTG exposure was periconception for 326 (64.9%) infants, later in trimester 1 for 36 (7.2%) and in trimester 2/3 for 140 (27.9%); 6 had unknown timing of exposure. There were 21 infants with birth defects (4.1%, 95% CI 2.6, 6.2); one infant had 2 defects. The 22 defects were in the following systems: genitourinary (7), heart (4), limb (4 [polydactyly, 3]), gastrointestinal (2), chromosomal (1), other (4); no CNS defects were reported.

**Conclusion:** The prevalence rate for overall birth defects here is the same as recently reported from the Antiretroviral Pregnancy Registry for periconception exposure to DTG. Dolomite-EPPICC will continue to monitor use and safety of DTG-based regimens in pregnancy, noting that our sample size of periconception exposures is currently too small to exclude potential associations with rare birth defects like NTDs.

| mITT analysis | Total (n=101) | Detectable CMV viremia (n=43) | Undetectable CMV viremia (n=58) | p-value |
|---|---|---|---|---|
| Age, years, median (IQR) | 41 (31-47) | 41 (32-52) | 38.5 (31-47) | 0.460 |
| Sex, female, n (%) | 14 (13.9) | 6 (14.9) | 8 (13.8) | 1.000 |
| Baseline AIDS-defining event, n (%) | 42 (41.6) | 22 (51.2) | 20 (34.5) | 0.100 |
| Baseline HIV VL, copies/mL, median (IQR) | 367643.5 (79146-1245000) | 824869.5 (272000-2270000) | 173100 (65702-804000) | 0.001 |
| Baseline CMV-specific IgG positive, n (%) | 96 (95.05) | 43 (100.00) | 53 (91.38) | 0.070 |
| Baseline CD4+ TL, cells/mm3, median (IQR) | 33.5 (10.5-67.5) | 22 (10-48.3) | 38 (17.4-74.1) | 0.056 |
| Week 48 CD4+ TL, cells/mm3, median (IQR) | 226 (162.5-326) | 282 (182-377) | 200 (132-292.8) | 0.004 |
| Week 48 HIV VL <50 copies/mL, n (%) | 71 (70.3) | 24 (66.7) | 47 (88.7) | 0.016 |
| IRIS, n (%) | 11 (10.9) | 11 (25.6) | 0 (0) | <0.001 |
| CMV-related IRIS, n (%) | 5 (4.9) | 5 (11.6) | 0 (0) | 0.028 |
| New AIDS event, n (%) | 9 (8.9) | 7 (16.3) | 2 (3.5) | 0.035 |

## 679 RISK-BENEFIT TRADE-OFF FOR PREGNANCY AND INFANT OUTCOMES: DTG, EFV, TAF, AND TDF

**Sean Brummel**[1], Lauren Ziemba[1], Anne Coletti[2], Lameck Chinula[3], Chelsea Krotje[4], Renee Browning[5], Esau Joao[6], Mpho Raesi[7], James S. Ngocho[8], Linda Aurpibul[9], Lynda Stranix-Chibanda[10], Roger L. Shapiro[1], Jeff Stringer[3], Shahin Lockman[1]

*[1]Harvard TH Chan School of Public Health, Boston, MA, USA, [2]FHI 360, Durham, NC, USA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [5]National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, [6]Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil, [7]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [8]Kilimanjaro Christian Medical Centre, Moshi,*

*Tanzania, [9]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand, [10]University of Zimbabwe, Harare, Zimbabwe*

**Background:** Understanding the risk-benefit trade-off for pregnancy and infant outcomes in clinical trials of pregnant women is complex due to multiple outcomes of interest. Clinical trials often summarize risks and benefits in separate analyses, which can be misleading. Alternatively, risk and benefit can be compared by arms using a desirability of outcome ranking (DOOR) with weights to account for severity. We employed this strategy using data from the IMPAACT 2010 (VESTED) trial.

**Methods:** 643 pregnant women living with HIV in 9 countries were randomized in 2018-2019 to one of three antiretroviral treatment arms: dolutegravir (DTG)+emtricitabine (FTC)/tenofovir alafenamide (TAF); DTG+FTC/tenofovir disoproxil fumarate (TDF); or efavirenz (EFV)/FTC/TDF. Mother-infant (MI) pair adverse outcomes were grouped according to the most severe outcome experienced: 1) infant death, 2) spontaneous abortion or stillbirth, 3) infant HIV infection (benefit via reduction), 4) very preterm delivery (<32 weeks), 5) major congenital anomaly, 6) preterm delivery (<37 weeks), 7) small for gestational age (<10th percentile, SGA), 8) infant hospitalization, and 9) infant grade 3 or 4 adverse event. Ordinal logistic regression was used to compare the odds of a more severe outcome across arms. Supplementary analyses weighted the ranked outcome according to the study team's belief of their relative severity using a tipping point method.

**Results:** 79/216 (37%), 93/213 (44%), and 101/211 (48%) MI pairs experienced at least one of the ranked outcomes in the DTG+FTC/TAF, DTG+FTC/TDF, and EFV/FTC/TDF arms, respectively. Ordinal logistic regression resulted in a better risk-benefit trade-off for DTG+FTC/TAF compared to EFV/FTC/TDF (OR=0.60, 95% confidence interval(CI):0.42, 0.88). In the severity-weighted analysis, DTG+FTC/TAF had a better risk-benefit trade-off relative to DTG+FTC/TDF (OR=0.64, 95%CI:0.49, 0.84) and EFV/FTC/TDF (OR=0.28, 95%CI:0.21, 0.36); DTG+FTC/TDF had a better risk-benefit trade-off relative to EFV/FTC/TDF (OR=0.41, 95%CI:0.32, 0.53).

**Conclusion:** The risk-benefit trade-off was clearer with these ranked outcome analyses, compared to the many separate previously reported analyses which favored different arms for outcomes of different severity in IMPAACT 2010. Overall, DTG+FTC/TAF provided the best and clearest risk-benefit trade-off when more severe outcomes were given more weight. Similarly, DTG+FTC/TDF had a better risk-benefit profile than EFV/FTC/TDF.

**Table: Ordinal Logistic Odds Ratios Summarizing the Risk-Benefit Trade-Off for the Ranked IMPAACT 2010 Outcome**

| Comparison | Ordinal Logistic Regression | | Severity Weighted Ordinal Logistic Regression | |
|---|---|---|---|---|
| | Odds Ratio (95% CI) | P-value | Odds Ratio (95% CI) | P-value |
| DTG+FTC/TAF vs. DTG+FTC/TDF | 0.73 (0.50, 1.06) | 0.095 | 0.64 (0.49, 0.84) | 0.0013 |
| DTG+FTC/TAF vs. EFV/FTC/TDF | 0.60 (0.42, 0.88) | 0.0077 | 0.28 (0.21, 0.36) | <0.0001 |
| DTG+FTC/TDF vs. EFV/FTC/TDF | 0.83 (0.58, 1.19) | 0.30 | 0.41 (0.32, 0.53) | <0.0001 |

## 680 ADVERSE OUTCOMES IN SUBSEQUENT PREGNANCIES IN THE IMPAACT 2010 TRIAL

**Lee Fairlie**[1], Sean Brummel[2], Lauren Ziemba[2], Anne Coletti[3], Lameck Chinula[4], Roger L. Shapiro[2], Jeff Stringer[5], Renee Browning[6], Nahida Chakhtoura[7], Blandina T. Mmbaga[8], Tsungai P. Mhembere[9], Ayotunde Omoz-Oarhe[10], Beatrice Naggadya1[1], Megeshinee Naidoo1[2], Shahin Lockman1[3]
*[1]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]FHI 360, Durham, NC, USA, [4]University of North Carolina Project–Malawi, Lilongwe, Malawi, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [7]National Institute of Child Health and Human Development, Bethesda, MD, USA, [8]Kilimanjaro Christian Medical Centre, Moshi, Tanzania, [9]University of Zimbabwe Clinical Trials Research Centre, Harare, Zimbabwe, [10]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [11]Baylor College of Medicine Children's Foundation, Kampala, Uganda, [12]Centre for the AIDS Programme of Research in South Africa, Durban, South Africa, [13]Brigham and Women's Hospital, Boston, MA, USA*

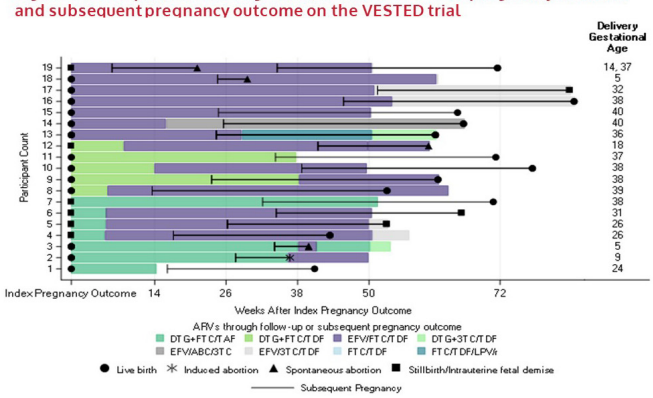
**Background:** Few studies have prospectively captured pregnancy outcomes among women living with HIV (WLHIV) who conceive on antiretroviral treatment (ART).

**Methods:** IMPAACT 2010 (VESTED) enrolled 643 WLHIV at 14-28 weeks gestational age in 9 countries. Women were randomized to start ART with dolutegravir (DTG) plus emtricitabine (FTC)/tenofovir alafenamide (TAF); DTG+FTC/tenofovir disoproxil fumarate (TDF); or efavirenz (EFV)/FTC/TDF. Due to recommendations at the time, women who did not wish to take effective contraception following delivery were required to switch from DTG to another antiretroviral (usually EFV) during the 50 weeks of postpartum study follow-up. We describe adverse pregnancy outcomes in women who became pregnant during postpartum follow-up (subsequent pregnancy): spontaneous abortion (<20 weeks), stillbirth (≥20 weeks), preterm delivery (<37 weeks), small for gestational age (SGA; <10th centile) and neonatal death (≤28 days).

**Results:** Nineteen (3%) of 643 women had 20 subsequent pregnancies on-study and were taking the following ART at conception: DTG+FTC/TAF (3), DTG+FTC/TDF (2), EFV/FTC/TDF (11, 1 woman with 2 pregnancies), non-study ART (2) and no ART (1). Only 12/20 (60%) subsequent pregnancies resulted in live birth; 4/20 (20%) spontaneous abortions, 3/20 (15%) stillbirths, and 1/20 (5%) induced abortion. Three (25%) liveborn infants were preterm (24, 26 and 36 weeks' gestation). Thus, at least one adverse pregnancy outcome occurred in 11/20 (58%) subsequent pregnancies, more frequently with EFV/FTC/TDF at conception (8 [67%] of 12 pregnancies) than with DTG-ART at conception (1/4 women) [Figure]. Our sample size was too small to formally test differences in outcomes of subsequent pregnancies by regimen. Of the 7 women who experienced spontaneous abortion or stillbirth in the subsequent pregnancy, 4 had experienced a stillbirth and 1 a neonatal death as outcomes of the earlier index pregnancy (the pregnancy at enrolment to the VESTED trial).

**Conclusion:** Adverse pregnancy outcomes were very common in this cohort of WLHIV who conceived on ART in the VESTED trial, particularly in women with recent prior pregnancy loss (potentially at higher risk for repeat adverse pregnancy outcome), however numbers were small. This finding should be considered in analyses of incident pregnancies occurring in trial participants. Data from larger similar cohorts of women are needed, to elucidate factors associated with adverse pregnancy outcomes in WLHIV.

Figure 1: Description of ART regimens, index VESTED trial pregnancy outcome and subsequent pregnancy outcome on the VESTED trial




## 681 SOME InSTIs INDUCE TOXICITY AND DIFFERENTIATION IN HUMAN EMBRYONIC STEM CELLS

New Investigator Scholar

**Marie-Soleil R. Smith**[1], Ronil Patel[1], Lou Martineau[2], Helene C. Cote[1]
*[1]University of British Columbia, Vancouver, Canada, [2]Ecole d'Ingénieurs de l'Université d'Angers, Angers, France*

**Background:** Approximately 1.1 million children are exposed to ARVs in utero each year. ARV safety is not fully characterized during pregnancy, especially if recently approved. The Tsepamo study reported a risk of neural tube defects in infants exposed to dolutegravir (DTG) from conception, suggesting that early fetal exposure may be detrimental. Our objective was to characterize the effects of four InSTIs in two human embryonic stem cell (hESC) lines, with respect to markers of pluripotency, early differentiation, and cellular healt

**Methods:** H9 and CA1S hESCs (n=6 and n=3 independent experiments, respectively) were exposed to DTG, cabotegravir (CAB), bictegravir (BIC), or raltegravir (RAL) at doses ranging from 0.01X to 1X peak plasma drug concentrations ($C_{max}$) or DMSO diluent control. After three days, hESCs were assessed via flow cytometry for cell viability, apoptosis, and two markers of pluripotency, specifically SSEA-3 (lost early in differentiation) and TRA-1-60 (a later marker). Cells treated with 0.5X $C_{max}$ were further examined for markers of differentiation towards the three germ layers via RT-qPCR. Paired t-tests were employed to compare InSTIs to DMSO controls.

**Results:** H9 hESCs exposed to DTG, CAB, and BIC at ≥0.5X $C_{max}$ had ≥2-fold decreased proliferation (p≤0.04). DTG and BIC exposure at 1X $C_{max}$ led to reduced

viability ($p<0.001$) and increased apoptosis ($p\leq0.001$). Similar trends were seen in CA1S hESCs exposed to ≥0.5X $C_{max}$ DTG, CAB, and BIC, where hESC proliferation decreased ≥2-fold; BIC exposure also decreased viability and increased apoptosis. H9 hESCs exposed to ≥0.5X $C_{max}$ DTG and CAB and 1X $C_{max}$ BIC showed a ≥20% decrease in SSEA-3 ($p\leq0.02$) and TRA-1-60 ($p\leq0.03$) expression. Further, expression of early mesendoderm lineage genes appears increased with exposure to ≥0.5X $C_{max}$ BIC, CAB, and DTG. The CA1S hESCs had a ≥75% decrease in SSEA-3 but no effect on TRA-1-60 with exposure to ≥0.5X $C_{max}$ DTG and CAB; no gene expression trends were noted. In both hESC lines, RAL did not induce any cytotoxicity or differentiation, regardless of dose exposure.

**Conclusion:** Even at sub-clinical concentrations, some InSTIs induce cytotoxicity and differentiation in hESCs. Given their use in first-line ARV regimens, including by women of reproductive age or pregnant, it is imperative to elucidate their long-term safety in the context of pregnancy and embryonic development. These data also indicate that RAL appears to show a safe profile, a reassuring finding that warrants further investigation.

## 682 IMPACT OF MATERNAL HIV/HBV COINFECTION ON PREGNANCY AND INFANT OUTCOMES

**Flavia K. Matovu**[1], Camlin Tierney[2], Audrey Chang[2], Dhayendre Moodley[3], Vani Govender[3], Tichaona Vhembo[4], Kathleen George[5], Neaka Z. Mohtashemi[6], Philippa Musoke[1], Dingase Dula[7], Nahida Chakhtoura[8], Marion Peters[9], Mary G. Fowler[10], Judith S. Currier[6], Debika Bhattacharya[6]

*[1]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Centre for the AIDS Programme of Research in South Africa, Durban, South Africa, [4]University of Zimbabwe, Harare, Zimbabwe, [5]FHI 360, Durham, NC, USA, [6]University of California Los Angeles, Los Angeles, CA, USA, [7]Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi, [8]National Institutes of Health, Bethesda, MD, USA, [9]Northwestern University, Chicago, IL, USA, [10]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

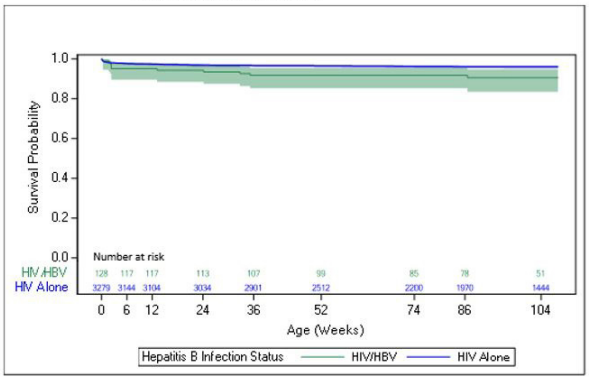
**Background:** The impact of maternal HIV/HBV coinfection on the risk of adverse pregnancy and infant outcomes remains understudied. We compared adverse pregnancy and infant outcomes among women living with HIV/HBV versus HIV alone, randomized antepartum to three of antiretroviral (ARV) perinatal transmission regimens in the IMPAACT PROMISE study.

**Methods:** ARV-naïve pregnant women with HIV from Africa and India were randomized to -zidovudine (ZDV) + intrapartum nevirapine, 3TC/ZDV+LPV/r, or FTC/TDF+LPV/r. Randomizations for women with HIV/HBV mirrored the main study and follow-up of infants for this analysis was up to 2 years. Associations between HIV/HBV coinfection and pregnancy and infant outcomes were assessed by logistic (odds ratio (aOR)), linear, and cox proportional hazards a(HR) regression, adjusted for randomized arm, baseline age, $log_{10}$HIV-1 RNA, CD4 count, and geographic region. HBV was defined as HBsAg positive. Adverse pregnancy outcome (APO) was a composite of low birth weight (<2500g), preterm delivery (<37 weeks), spontaneous abortion (<20 weeks), stillbirth (≥20 weeks) or congenital anomaly. We further compared HBeAg positive/negative subgroups to HIV infection alone.

**Results:** Between April 2011-October 2014, 3537 mother-infant pairs were analyzed, of whom 138 women had HBV/HIV coinfection. Thirty-four of 131 (26%) women were HBeAg(+). APOs were numerically higher in the HBV/HIV group vs HIV alone (33.3% vs 28.2%; aOR 1.31, 95%CI: 0.89, 1.91). HIV/HBV women who were HBeAg(+) had a significantly higher risk of APOs (aOR 2.65, 95% CI: 1.28, 5.47), vs HIV alone. Eleven (8.6% of 128) infant deaths were observed in the HIV/HBV group and 120 (3.7% of 3279) in the HIV alone groups. Infants of HIV/HBV women were at significantly higher risk for mortality (HR 2.39, 95%CI: 1.21, 4.22)(Figure). Seventy-two of 131 (55%) infant deaths occurred within 28 days. No differences were apparent between HBV/HIV and HIV alone groups in time to HIV acquisition, mean infant weight at birth and one year, WHO length- and head circumference -for-age Z-scores at one year. The above associations did not appear to differ by treatment arm.

**Conclusion:** Maternal HBV/HIV coinfection, when compared to HIV infection alone, was associated with a higher risk of APO and significantly higher infant mortality. The risk of APOs was increased in women with HBeAg. Our findings underscore the importance of early detection of HBV and HBeAg to help manage APO.

**Figure: Time to Infant Death**




Hepatitis B infection status refers to maternal HBV status.

## 683 HIV-RELATED DIFFERENCES IN PLACENTAL IMMUNOLOGY: DATA FROM THE PRACHITi COHORT

**Jyoti S. Mathad**[1], Ramesh Bhosale[2], Mallika Alexander[3], Shilpa Naik[2], Vandana Kulkarni[2], Lisa Marie Cranmer[4], Andrea Chalem[1], Jin Liu[5], Jun Lei[5], Anna Chudnovets[5], Anguo Liu[5], Rupak Shivakoti[6], Amita Gupta[5], Irina Burd[5]

*[1]Weill Cornell Medicine, New York, NY, USA, [2]Byramjee Jeejeebhoy Government Medical College, Pune, India, [3]Byramjee Jeejeebhoy Government Medical College-Johns Hopkins Clinical Trials Unite, Pune, India, [4]Emory University, Atlanta, GA, USA, [5]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [6]Columbia University, New York, NY, USA*

**Background:** HIV-exposed and uninfected (HEU) infants have a higher risk of death than HIV-unexposed and uninfected infants, mostly from infections. We hypothesized that maternal HIV infection, even when virally suppressed, affects placental immunology and expression of FcRn, a receptor that facilitates maternal-fetal transmission of antibodies.

**Methods:** We conducted an observational study of 234 pregnant women with and without HIV in Pune, India (PRACHITi). Participants were enrolled during 2nd trimester and followed until 1 year postpartum. A convenience sample of 42 women had placenta collected at delivery. FcRn expression was analyzed by Western blot (normalized by GADPH) and compared using Image J. Placental CD4+ and CD8+ T-cell abundance was assessed by immunofluorescent counting per high powered field (5 fields/slide). Placental expression of TGFβ, IL-6, IL-10, and IL-12 was measured by mRNA array. Continuous data were tested for normality with outliers identified using Grubb's test. The one-way analysis of variance with Tukey post hoc test and chi-square analysis were used to compare categorical variables.

**Results:** Of 42 placentae, 38 were of sufficient quality to analyze. The median gestational age at delivery was 38.3 weeks (IQR: 37.5-39.1). Of 18 women with HIV, all were on combined antiretroviral therapy (cART) with a median CD4 of 455 cells/$mm_3$ at entry and 429 cells/$mm_3$ at delivery. Ten (55%) were virally suppressed (≤100 copies/mL); of those who were detectable, the median viral load was 151 (IQR: 118.15–539334). Relative placental FcRn expression was lower in women with HIV compared to without (median 0.54 vs. 0.84, $p=0.01$) (Fig 1A) and was not associated with CD4 or viral load. Compared to women without HIV, those with HIV had no differences in placental CD4+ T-cells or cytokine expression but had a significantly higher abundance of placental CD8+ T-cells (Fig 1B). Placental CD8+ T-cell numbers were similar in women with and without viral suppression (Fig 1C).

**Conclusion:** We found that women with HIV, even when virally suppressed, have lower placental FcRn expression, which may result in lower transmission of maternal antibodies. Women with HIV also had increased placental abundance of CD8+ T-cells, which has been associated with placental inflammation and poor infant outcomes (eg, preterm birth). Taken together, our data suggest that maternal HIV causes placental immune dysregulation that is not completely reversed by cART and may contribute to the poorer outcomes of HEU infants.

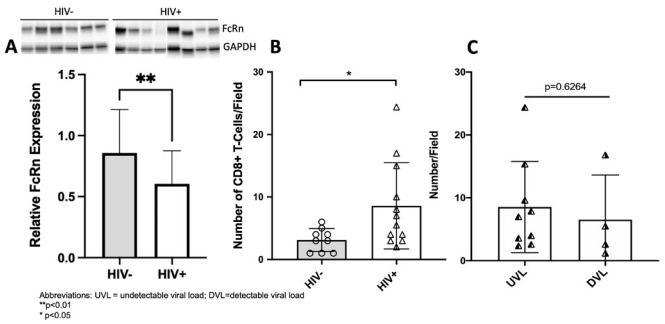



**Figure**. Placenta from women with HIV had significantly lower FcRn expression than women without HIV (panel A). Placental abundance of CD8+ T-cells was higher in women with HIV compared to women without HIV (panel B), but was unaffected by viral suppression (p=0.60) (panel C).

## 684 PERINATAL HIV-1 TRANSMISSION IN FRANCE: U=U FOR MOTHERS ON ART FROM CONCEPTION

**Jeanne Sibiude**[1], Jerome Le Chenadec[2], Laurent Mandelbrot[1], Alexandre Hoctin[2], Catherine Dollfus[3], Albert Faye[4], Eida Bui[5], Emmanuelle Pannier Metzger[6], Jade Ghosn[7], Valérie Garrait[8], Véronique Avettand-Fenoël[9], Pierre Frange[9], Josiane Warszawski[2], Roland Tubiana[10]

*[1]Hôpital Louis-Mourier, Colombes, France, [2]Institut National de la Santé et de la Recherche Médicale, Le Kremlin-Bicetre, France, [3]Trousseau Hospital, Paris, France, [4]Robert–Debre Hospital, Paris, France, [5]Saint-Antoine Hospital, Paris, France, [6]Cochin Hospital, Paris, France, [7]Hôpital Bichat-Claude-Bernard, Paris, France, [8]Centre Hospitalier Intercommunal de Créteil, Créteil, France, [9]Necker Hospital, Paris, France, [10]Hôpitaux Universitaires Pitié Salpêtrière, Paris, France*

**Background:** Antiretroviral therapy (ART) is remarkably effective to prevent perinatal transmission (PT) of HIV-1. We sought to evaluate the transmission rate in population in a context of generalized ART before conception.

**Methods:** The analysis included 14,630 HIV-1-infected mothers- delivering from 2000 to 2017 in centers participating in the nationwide prospective multicenter French Perinatal Cohort (ANRS-EPF). PT was analyzed according to time period, timing of ART initiation, plasma viral load (pVL) in the first trimester of pregnancy and at delivery, and gestational age at birth. No woman breastfed in our cohort.

**Results:** The proportion of women receiving combined ART at delivery increased from 67.7% in 2000-2005 to 97.7% in 2006-2010, and 99.2% in 2011-2017 (p<0.001), as did the proportion of those already on ART before conception (28.3% in 2000-2005 vs 65.8% in 2011-2017, p<0.001) and the proportion of women treated from conception with pVL below limit of quantification (BLOQ) or <50 copies/mL near delivery (70% in 2000-2005, 89% in 2006-2010, 93% in 2011-2017 (p<0.001)). PT decreased from 1.1% in 2000-2005 (58/5,123), to 0.7% in 2006-2010 (30/4600), and 0.2% in 2011-2017 (10/4907; p<0.001). Restricting the analysis to women on ART at conception, PT decreased from 0.42% in 2000-2005 (6/1434), to 0.03% in 2011-2017 (1/3117), p=0.007 (Table). Among women treated at conception, whatever the type of ART combination, no PT was observed if maternal pVL was BLOQ or <50 copies/mL near delivery (0/5482, 95% CI [0-0.07]). In this cohort, there was no case of PT if the 1st trimester viral load was BLOQ or < 50 copies/mL (0/2358), 95%CI [0-0.16]. In the overall population, PT rate was higher following severe preterm deliveries (<32WG) 2.06%, than in moderate preterm (32WG-36WG) 1.34%, or in term deliveries 0.54% (p<0.001). However, this association was not found in 2011-2017, where a higher proportion of women were virally suppressed from the first trimester.

**Conclusion:** In the absence of breastfeeding, and in the French context of free access to ART and monthly pVL assessment suppressive ART initiated before pregnancy and continued throughout the pregnancy can eliminate perinatal transmission of HIV. The challenge is now to improve early engagement and sustained adherence in health care systems.

**Table. HIV-1 perinatal transmission rates according to time period, timing of ART initiation and plasma viral load near delivery.**

| | Transmission rate 2000-2005 N=4946 | | Transmission rate 2006-2010 N=4403 | | Transmission rate 2011-2017 N=4705 | | P[a] |
|---|---|---|---|---|---|---|---|
| **Timing of ART initiation** | % (95% CI) | n/N | % (95% CI) | n/N | % (95% CI) | n/N | |
| Before conception | **0.42** (0.15 - 0.91) | (6 / 1434) | **0.10** (0.01 - 0.35) | (2 / 2055) | **0.03** (0.00 - 0.18) | (1 / 3117) | 0.007 |
| 1st Trimester | **0.31** (0.01 - 1.72) | (1 / 322) | **0.80** (0.17 - 2.32) | (3 / 375) | **0.44** (0.05 - 1.59) | (2 / 452) | 0.68 |
| 2nd Trimester | **1.01** (0.59-1.61) | (17 / 1687) | **0.65** (0.31 - 1.19) | (10 / 1541) | **0.44** (0.12 - 1.11) | (4 / 919) | 0.27 |
| 3rd Trimester | **1.53** (0.97 - 2.29) | (23 / 1503) | **2.55** (1.28 - 4.51) | (11 / 432) | **0.92** (0.11 - 3.29) | (2 / 217) | 0.26 |
| **Among women treated at conception and according to plasma viral load near delivery[b]** | | | | | | | |
| **Viral load near delivery (Cops/mL )** | % (95% CI) | n/N | % (95% CI) | n/N | % (95% CI) | n/N | p |
| < 50 | **0.00** (0.00 - 0.50) | (0/741) | **0.00** (0.00 - 0.22) | (0/1700) | **0.00** (0.00 - 0.13) | (0/2806) | 0.66 |
| Below limit of quantification, threshold > 50 | **0.00** (0.00 - 2.03) | (0/180) | **0.00** (0.00 - 7.11) | (0/50) | **0.00** (0.00 - 52.2) | (0/5) | 1 |
| 50 - 399 | **0.00** (0.00 - 2.25) | (0 / 162) | **0.59** (0.01 - 3.25) | (1 / 169) | **0.00** (0.00 - 2.11) | (0 / 173) | 0.52 |
| >=400 | **2.60** (0.96 - 5.57) | (6 / 231) | **2.08** (0.05 - 11.1) | (1 / 48) | **1.96** (0.05 - 10.4) | (1 / 51) | 1 |

a : p-value : Fisher exact test comparing transmission across time periods. b : the cutoffs for HIV RNA detection changed during the 18-year period, from 500 to 50 copies/mL, <50 copies/mL becoming the standard after 2005, and < 20 copies/mL in several laboratories. In this study, viral suppression was defined for the analysis as viral load < 50 copies/mL, or under the threshold (BLOQ) if it was above 50 copies/mL. viral load closest to delivery, between 90 days before delivery and 7 days after delivery.

## 685 WITHDRAWN

## 686 PBPK MODELING OF LONG-ACTING INJECTABLE CABOTEGRAVIR IN PREGNANCY

New Investigator Scholar

**Shakir A. Atoyebi**[1], Fazila S. Bunglawala[1], Nicolas Cottura[1], Maiara C. Montanha[1], Marco Siccardi[1], Catriona Waitt[1]

*[1]University of Liverpool, Liverpool, UK*

**Background:** Long acting injectable (LAI) cabotegravir (CAB) has recently been approved for the treatment of HIV in adults. However, there are currently no adequate data to inform its administration during pregnancy. The aim of this study was to apply physiologically-based pharmacokinetic (PBPK) modelling to predict the PK of LAI CAB in pregnancy.

**Methods:** An adult PBPK model was modified in SimBiology (MATLAB R2019a) to represent a pregnant population; pregnancy-induced anatomical, physiological, and metabolic changes (eg, progesterone-mediated induction, organ blood-flow rates etc.) known to influence drug PK were incorporated. Prior to running simulations in pregnant patients, the non-pregnant model was qualified against clinical PK data in adults for single doses of 30 mg oral, 400 mg and 800 mg intramuscular (IM) CAB, and 400 mg oral raltegravir (RAL). Clinical PK data for probe substrate RAL in pregnant women was used to validate the activity of key enzyme UGT1A1 during pregnancy. The qualified pregnancy model was used to predict the PK of single doses of CAB (30 mg oral, LAI 400 mg & 600 mg IM) across different trimesters in pregnancy.

**Results:** Absolute average fold errors (AAFE) of the mean PK parameters for oral RAL and CAB in adults were between 1.0-1.9 fold, and <1.5 fold, respectively. IM CAB simulations in non-pregnant adults successfully passed model qualification criteria with AAFEs between 1.0-1.9 fold. In the second and third trimester of pregnancy, AAFE values of oral RAL were within the 2-fold acceptance criteria, providing confidence in model simulations for CAB. Predicted elimination kinetics of CAB 400mg IM were closely related to observed data. The predicted geometric mean of plasma exposures in pregnant and non-pregnant patients were comparable for each of the single doses of CAB that were examined in this study (Table 1).

**Conclusion:** These data suggest dosage adjustments are not necessary for IM LA CAB to maintain therapeutic concentrations and clinical efficacy during pregnancy. This approach could be utilised to predict the risk related to altered PK during pregnancy for IM LA therapy and support the design of future clinical trials in pregnant women.

Table 1: Simulated PK of CAB and RAL in pregnant and non-pregnant adults.

| PK Variable | Observed vs Simulated in Non-pregnant Adults | | Simulated T1 | Simulated T2 | Simulated T3 |
|---|---|---|---|---|---|
| | Observed CAB 30 mg PO | Simulated CAB 30 mg PO | CAB 30 mg PO | CAB 30 mg PO | CAB 30 mg PO |
| $C_{max}$ (µg/mL) | 3.61 | 3.07 | 4.22 | 4.18 | 4.19 |
| $AUC_{0-\infty}$ (µg.hr/mL) | 146 | 98.2 | 134 | 127 | 126 |
| | Observed CAB 400 mg / 600 mg IM | Simulated CAB 400 mg / 600 mg IM | CAB 400 mg / 600 mg IM | CAB 400 mg / 600 mg IM | CAB 400 mg / 600 mg IM |
| $C_{4weeks}$ (µg/mL) | 0.40 / - | 0.74 / 1.12 | 0.78 / 1.16 | 0.77 / 1.17 | 0.76 / 1.13 |
| $C_{max}$ (µg/mL) | 0.70 / - | 0.89 / 1.34 | 0.93 / 1.38 | 0.91 / 1.39 | 0.91 / 1.35 |
| $AUC_{4weeks-4}$ (µg.hr/mL) | 290 / - | 534 / 806 | 561 / 833 | 550 / 838 | 549 / 811 |
| | Observed RAL 400 mg PO | Simulated RAL 400 mg PO | | Observed / Simulated RAL 400 mg PO [T2] * | Observed / Simulated RAL 400 mg PO [T3] * |
| $C_{12}$ (ng/mL) | 35.8 | 36.0 | | 62.1 / 52.8 | 64.0 / 48.0 |
| $C_{max}$ (ng/mL) | 1279 | 1997 | | 2250 / 1985 | 1770 / 1970 |
| $AUC_{0-12}$ (ng.hr/mL) | 4884** | 9281** | | 6600 / 9781 | 5400 / 9581 |

Data shown represent Geometric mean values. *Median values, **$AUC_{0-\infty}$, PO – oral, IM – intramuscular, CAB – Cabotegravir, RAL – Raltegravir, $C_{max}$ – Maximum plasma concentration, $C_{4weeks}$ – Plasma concentration at 4 weeks, $AUC_{4weeks-4}$ - Area under the plasma concentration-time curve till 4 weeks, $AUC_{0-\infty}$ - Area under the plasma concentration-time curve till infinity, T1 – PK values in First trimester, T2 – PK values in Second trimester, and T3 – PK values in Third trimester

## 687 PREGNANCY HEMOGLOBIN A1c AND GLUCOSE WITH DTG VS EFV, TDF VS TAF: IMPAACT 2010

**Lameck Chinula**[1], Evan Goldberg[2], Lauren Ziemba[2], Katie McCarthy[3], Chelsea Krotje[4], Kevin Knowles[4], Jyoti S. Mathad[5], Maria Leticia Santos Cruz[6], Risa M. Hoffman[7], Patrick Jean-Philippe[8], Tsungai Chipato[9], Deo Wabwire[10], Judith S. Currier[7], Shahin Lockman[11], Nahida Chakhtoura[12]

*[1]University of North Carolina Project–Malawi, Lilongwe, Malawi, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]FHI 360, Durham, NC, USA, [4]Frontier Science Foundation, Inc., Amherst, NY, USA, [5]Weill Cornell Medicine, New York, NY, USA, [6]Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil, [7]University of California Los Angeles, Los Angeles, CA, USA, [8]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, [9]University of Zimbabwe Clinical Trials Research Centre, Harare, Zimbabwe, [10]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [11]Brigham and Women's Hospital, Boston, MA, USA, [12]National Institute of Child Health and Human Development, Bethesda, MD, USA*

*Background: In IMPAACT 2010, a trial comparing 3 antiretroviral treatment (ART) regimens initiated in pregnancy, dolutegravir (DTG)--particularly in combination with tenofovir alafenamide (TAF)--was associated with more weight gain but better pregnancy outcomes than ART containing efavirenz (EFV) or tenofovir disoproxil fumarate (TDF). The impact of these weight gain patterns during pregnancy on gestational diabetes is unknown. We evaluated glycated hemoglobin (HbA1c) and glucose in study participants.*

*Methods: 643 pregnant women with HIV in 9 countries were randomized 1:1:1 to start open-label DTG+emtricitibine (FTC)/TAF, DTG+FTC/TDF, or EFV/FTC/TDF at 14-28 weeks' gestation. Following a protocol amendment partway through the trial, we sampled maternal HbA1c and random glucose at study entry, 12 weeks after enrolment (antepartum) and delivery; and neonatal glucose within 48 hours of birth. By-arm differences in mean maternal HbA1c and glucose levels and time-averaged area under the curve (AUC) and infant glucose levels were evaluated using student's t-tests. We compared the proportion of women with post-baseline HbA1c ≥5.7% (prediabetic) between arms using Wald Tests and described the proportion of women with HbA1c ≥6.5% (defined as diabetic).*

**Results: 348** mothers and 65 infants had HbA1c and/or glucose result available (114 in the DTG+FTC/TAF; 116 in the DTG+FTC/TDF; and 118 in the EFV/FTC/TDF arms); 78% enrolled in Africa. Maternal enrolment medians were: age 25.9 years, gestational age 21.5 weeks, BMI 24.1 kg/cm2, HIV-1 RNA 3.1 $log_{10}$, and CD4 466 cells/$mm_3$. No women had a diabetes diagnosis at entry. Maternal mean HbA1c levels (Table) and mean time-averaged HbA1c AUC did not differ significantly between arms. Seven percent of women in the DTG+FTC/TAF arm, 6.0% in the DTG+FTC/TDF arm, and 3.4% in the EFV/FTC/TDF arm had at least one post-baseline HbA1c ≥5.7% (p≥0.21 for between-arm comparisons). One woman in the DTG+FTC/TAF arm developed HbA1c ≥6.5% post-baseline. The DTG+FTC/TDF arm had a higher mean time-averaged AUC glucose vs the EFV/FTC/TDF arm (mean difference [95% CI]: 0.17 [0.00, 0.34] mmol/L). Mean infant glucose levels ≤48 hours of birth were similar by arm.

**Conclusion: In** this randomized trial with modest sample sizes of participants assessed for HbA1c and random glucose, we did not observe significant differences in maternal HbA1C by ART regimen, nor clinically meaningful differences in maternal or infant random glucose.

**Table: Maternal antepartum HbA1c and maternal and infant random glucose by randomized arm**

| | DTG+F/TAF | DTG+F/TDF | EFV+F/TDF | Treatment Arm Comparison | Comparison Difference (95% CI)* | P-value |
|---|---|---|---|---|---|---|
| Mean (sd) HbA1c at delivery (%) | 5.14 (0.31) | 5.11 (0.38) | | DTG+F/TAF vs DTG+F/TDF | 0.03 (-0.06, 0.12) | 0.51 |
| | | 5.11 (0.38) | 5.10 (0.32) | DTG+F/TDF vs EFV+F/TDF | 0.01 (-0.09, 0.10) | 0.88 |
| | 5.14 (0.31) | | 5.10 (0.32) | DTG+F/TAF vs EFV+F/TDF | 0.04 (-0.05, 0.12) | 0.37 |
| % (n/N) women with HbA1C ≥5.7% at week 12 or delivery | 7.0% (8/114) | 6.0% (7/116) | | DTG+F/TAF vs DTG+F/TDF | -1.0% (-7.9%, 5.8%) | 0.76 |
| | | 6.0% (7/116) | 3.4% (4/118) | DTG+F/TDF vs EFV+F/TDF | -2.6% (-8.9%, 3.2%) | 0.34 |
| | 7.0% (8/114) | | 3.4% (4/118) | DTG+F/TAF vs EFV+F/TDF | -3.6% (-10.2%, 2.4%) | 0.21 |
| Mean (sd) time-averaged maternal glucose AUC (mmol/L) | 4.66 (0.72) | 4.80 (0.66) | | DTG+F/TAF vs DTG+F/TDF | -0.14 (-0.32, 0.04) | 0.13 |
| | | 4.80 (0.66) | 4.63 (0.64) | DTG+F/TDF vs EFV+F/TDF | 0.17 (0.00, 0.34) | 0.045 |
| | 4.66 (0.72) | | 4.63 (0.64) | DTG+F/TAF vs EFV+F/TDF | 0.03 (-0.15, 0.21) | 0.72 |
| Mean (sd) infant glucose within 48 hours of birth (mmol/L) | 3.43 (1.09) | 3.40 (1.06) | | DTG+F/TAF vs DTG+F/TDF | 0.03 (-0.63, 0.69) | 0.93 |
| | | 3.40 (1.06) | 3.49 (1.03) | DTG+F/TDF vs EFV+F/TDF | -0.09 (-0.72, 0.53) | 0.77 |
| | 3.43 (1.09) | | 3.49 (1.03) | DTG+F/TAF vs EFV+F/TDF | -0.06 (-0.74, 0.62) | 0.86 |

*Comparisons included difference in means for continuous outcomes and difference in proportions for binary outcomes.

## 688 WEIGHT GAIN WITH RALTEGRAVIR VS EFAVIRENZ DURING PREGNANCY

**Conrado M. Coutinho**[1], Meredith Warshaw[2], Geraldo Duarte[1], Alice M. Stek[3], Avy Violari[4], Cristina B. Hofer[5], Jaime Deville[6], James S. Ngocho[7], José H. Pilotto[8], Mario D. Correa[9], Trevon Fuller[6], Nahida Chakhtoura[10], Mark Mirochnick[11], Esau Joao[12]

*[1]University de São Paulo Ribeirão Preto, Ribeirão Preto, Brazil, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University of Southern California, Los Angeles, CA, USA, [4]University of Witwatersrand, Johannesburg, South Africa, [5]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [6]University of California Los Angeles, Los Angeles, CA, USA, [7]Kilimanjaro Christian Medical Centre, Moshi, Tanzania, [8]Hospital Geral de Nova Iguaçu, Rio de Janeiro, Brazil, [9]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [10]National Institute of Child Health and Human Development, Bethesda, MD, USA, [11]Boston University, Boston, MA, USA, [12]Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil*

**Background:** Gestational weight (wt) changes can affect pregnancy outcomes. While integrase inhibitor use has raised concerns of potential adverse metabolic effects and excessive wt gain, wt gain with raltegravir (RAL) use has not been adequately described in pregnancy. NICHD P1081 was a randomized trial comparing RAL and efavirenz (EFV) based combined antiretroviral therapy (cART) in antiretroviral (ARV) naïve pregnant women living with HIV in the second and third trimester. Participants from Argentina, Brazil, South Africa, Tanzania, Thailand, and the US were randomized 1:1 to receive a triple ARV regimen containing either RAL or EFV. The objectives of these post-hoc exploratory analyses were to compare antepartum changes in wt and body mass index (BMI) between treatment arms, and examine associations between wt gain and adverse pregnancy outcomes (APO).

**Methods:** These analyses examined 281 women with singleton pregnancies enrolled between 20 and 31 weeks gestational age (GA), on study for ≥4 weeks, with data on wt and delivery outcomes. Wt and BMI were analyzed as the rate of change per week from entry to delivery. Low rate of wt gain (WG) was defined as <0.18 kg/wk and high rate of WG as ≥0.59 kg/wk. Median rate of WG and BMI increase on EFV vs. RAL were compared using Kruskal-Wallis tests; the frequencies of low, normal and high rate of WG were compared using Fisher's exact test. Exact logistic regression analyses were used to investigate the association between WG category and APO (stillbirth, neonatal death,

preterm delivery <37 and <34 weeks, small and large for GA [SGA and LGA], or a composite APO). Tests used a 2-sided 5% significance level.

**Results:** Baseline characteristics were similar between EFV (N=137) and RAL (N=144) groups. RAL-based ARV regimen was associated with significantly higher antepartum wt gain (median 0.36 kg/wk vs. 0.29 kg/wk, p=0.01) and BMI increase (median 0.14 kg/m$^2$/wk vs. 0.11 kg/m$^2$/wk, p=0.01) compared to EFV-based treatment. Women on RAL were less likely to have low WG (18% vs. 36%) and more likely to have high WG (21% vs. 12%) (p=0.001). Women with low WG were significantly more likely to have SGA infants or to have composite APO than women with normal WG (Table). There were no significant differences in rates of APO between women with high versus normal WG.

**Conclusion:** Low rate of WG, which may be associated with adverse pregnancy outcomes, was less common with RAL-based treatment in ARV-naïve pregnant women compared to EFV-based cART.

**Table. Association of rate of antenatal weight gain with birth outcomes.**

| | N (column %) with outcome | | | Odds Ratio (95% Confidence Interval) | | | |
|---|---|---|---|---|---|---|---|
| Birth Outcome | Low rate (N=76) | Normal rate (N=158) | High rate (N=47) | Low vs. normal rate of weight gain | p-value | High vs. normal rate of weight gain | p-value |
| Composite outcome** | 32 (44%) | 35 (22%) | 13 (28%) | 2.7 (1.4, 5.2) | 0.002 | 1.3 (0.6, 3.0) | 0.55 |
| Stillbirth | 3 (4%) | 0 (0%) | 0 (0%) | 8.2 (1.2, >999.9) | 0.07 | N/A | N/A* |
| Neonatal death | 1 (1%) | 1 (1%) | 0 (0%) | 2.1 (0.0, 165.3) | >0.99 | N/A | N/A* |
| Preterm <37 weeks | 7 (10%) | 15 (9%) | 7 (15%) | 1.1 (0.4, 3.0) | >0.99 | 1.7 (0.5, 4.7) | 0.43 |
| Preterm <34 weeks | 2 (3%) | 3 (2%) | 4 (9%) | 1.5 (0.1, 13.8) | 0.96 | 4.8 (0.8, 33.7) | 0.10 |
| Small for gestational age | 21 (30%) | 20 (13%) | 7 (15%) | 3.0 (1.4, 6.4) | 0.003 | 1.2 (0.4, 3.2) | 0.85 |
| Large for gestational age | 4 (6%) | 16 (10%) | 2 (4%) | 0.5 (0.1, 1.8) | 0.43 | 0.4 (0.0, 1.8) | 0.34 |

* N/A: Not available (odds ratios and confidence intervals could not be estimated well due to very small numbers of events)
** Composite includes the occurrence of any of: stillbirth, neonatal death, preterm (<37 weeks) or small for gestational age (<10$^{th}$ percentile)

## 689 GESTATIONAL WEIGHT GAIN IN SOUTH AFRICAN PREGNANT WOMEN LIVING WITH HIV

**Hlengiwe P. Madlala**[1], Landon Myer[1], Azetta Fisher[1], Mushi Matjila[1], Gregory Petro[1], Zandile Maqwatini[1], Angela Bengtson[2]
*[1]University of Cape Town, Cape Town, South Africa, [2]Brown University, Providence, RI, USA*

**Background:** Concerns remain about DTG-associated weight gain, particularly among women. However, there are few data on gestational weight gain (GWG) among pregnant women living with HIV (WLH) initiating DTG vs EFV-based ART.

**Methods:** In a cohort of WLH and HIV- women in Cape Town, we investigated weights pre-pregnancy and in the 2nd (24-28w gestation) and 3rd (30-36w gestation) trimesters. WLH initiated TDF/XTC/EFV or TDF/XTC/DTG. Weights were self-reported pre-pregnancy and nurse-measured in the 2nd and 3rd trimesters. We estimated the rate of GWG as the weight difference between each of the two timepoints divided by the lapsed weeks (kg/week). We evaluated differences in rate of GWG by HIV and by ART regimen (DTG vs EFV) among women initiating ART post conception.

**Results:** In 244 women (117 HIV-, 127 WLH), the median age was 30y (IQR, 25-34) and 18% were primigravid. Among WLH, 50% (n=64) initiated ART post-conception (66% [n=42] DTG; 34% [n=22] EFV); there were no differences in baseline characteristics by ART regimen. Overall mean weight pre-pregnancy was 80kg (SD=18), 2nd trimester was 86kg (SD=19) and 3rd trimester was 89kg (SD=19). There was no difference in weight by HIV status pre-pregnancy (WLH 79 vs HIV- 81 kg, p=0.23), but WLH weighed less in the 2nd (84 vs 88 kg, p=0.05) and 3rd (86 vs 92 kg, p=0.01) trimesters compared to HIV- women. Women initiating DTG had non-significantly higher mean weights pre-pregnancy (81 vs 75 kg, p=0.20), 2nd (84 vs 79 kg, p=0.41) and 3rd (86 vs 81 kg, p=0.47) trimesters compared to those on post-conception EFV. WLH gained weight slower between pre-pregnancy and 2nd trimester (0.18 vs 0.26 kg/week, p=0.01), and 2nd and 3rd trimesters (0.26 vs 0.43 kg/week, p=0.01) than HIV- women. There were no differences in GWG rate by ART regimen between pre-pregnancy and 2nd trimester (DTG 0.11 vs EFV 0.18 kg/week, p=0.48), and 2nd and 3rd trimesters (DTG 0.20 vs EFV 0.29 kg/week, p=0.53).

**Conclusion:** WLH had lower weight and slower GWG compared to HIV- women. However, the rate of GWG between 2nd and 3rd trimesters for both WLH and HIV- women was above IOM recommendations. Post-conception DTG did not lead to faster GWG. Integration of weight management interventions with antenatal care services is needed to avert excess GWG-related adverse maternal health.

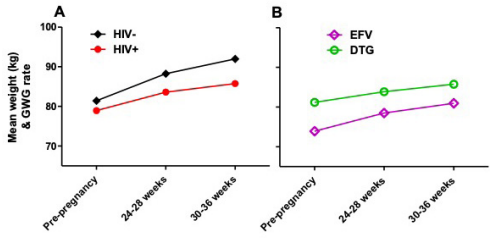



**Figure 1:** The dots on the plot show mean weights at pre-pregnancy, 2$^{nd}$ and 3$^{rd}$ trimesters, and the lines connecting the dots represent GWG rate between pre-pregnancy and 2$^{nd}$ trimester and between 2$^{nd}$ and 3$^{rd}$ trimesters. Panel A shows stratification by HIV status (117 HIV-, 127 WLH) and panel B by ART regimen initiated in pregnancy (42 DTG, 22 EFV).

## 690 UNIQUE PROFILE OF INFLAMMATION AND IMMUNE ACTIVATION IN PREGNANT US WOMEN WITH HIV

**Stephanie Shiau**[1], Denise Jacobson[2], Yanling Huo[2], Deborah Kacanek[2], Lynn M. Yee[3], David B. Williams[4], Lisa Haddad[5], Lena Serghides[6], Kathleen M. Powis[2], Paige L. Williams[2], Jennifer Jao[3]
*[1]Rutgers University, Piscataway, NJ, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Northwestern University, Chicago, IL, USA, [4]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA, [5]Population Council, New York, NY, USA, [6]University of Toronto, Toronto, Canada*

**Background:** Little is known about inflammation and immune activation during pregnancy in women living with HIV (WLHIV) on antiretroviral therapy (ART) compared to women who were HIV-seronegative (WHIV-), and how mode of HIV acquisition and/or type of ART may be associated with inflammation/immune activation in pregnant WLHIV.

**Methods:** Using data from the Surveillance Monitoring for ART Toxicities study of the Pediatric HIV/AIDS Cohort Study and a comparison group of WHIV-, we assessed associations between the following exposures with inflammation and immune activation in pregnancy: 1) HIV status, 2) mode of HIV acquisition [perinatally-acquired HIV (PHIV) vs. non-PHIV (NPHIV)], and 3) ART regimen. Biomarkers of inflammation [interleukin (IL)-6, high-sensitivity C-reactive protein (hsCRP), soluble (s) TNF-alpha receptor 1&2 (sTNFR1, sTNFR2)] and immune activation (sCD14, sCD163) were measured between 13-27 weeks' gestation by enzyme immunoassay. Generalized linear regression models with robust standard errors were fit to estimate the mean difference in log-transformed biomarker levels between groups, adjusted for potential confounders.

**Results:** We included 188 WLHIV (39 PHIV, 149 NPHIV) and 76 WHIV-. WLHIV were older (mean age 29 vs. 24 years), and more often Non-Hispanic Black (60 vs. 41%) than WHIV-. Among WLHIV, 32%, 31%, and 27% were on integrase strand transfer inhibitor (InSTI)-, protease inhibitor (PI)-, and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART, respectively, 6% were on ART consisting of ≥3 antiretroviral classes, and 67% had an HIV RNA level <50 copies/mL at the time of biomarker assessment. After adjusting for age, race/ethnicity, education, gravidity, pre-pregnancy/1st trimester BMI, 1st trimester tobacco/alcohol/illicit drug use, and sexually transmitted infections in pregnancy, WLHIV had higher IL-6, sTNFR1, sCD14, and sCD163 and lower sTNFR2, compared to WHIV-. Among WLHIV, sCD163 was higher in women with PHIV vs. NPHIV after also adjusting for HIV RNA level. Compared to WLHIV on InSTI-based ART, sCD163 was higher in WLHIV on PI-based ART after also adjusting for HIV RNA level and mode of HIV acquisition (see Table).

**Conclusion:** Maternal HIV status is associated with a distinct profile of inflammation and immune activation in pregnancy; immune activation may be more pronounced in those with PHIV and those on PI-based ART. Additional studies are needed to understand how this may affect maternal and infant outcomes.

**Table: Adjusted associations of maternal HIV status, mode of HIV acquisition, and ART regimen with log-transformed biomarker concentrations of inflammation and immune activation**

| Exposure | | Biomarker; Adjusted Estimated Mean Difference[1] (p-value) | | | | | |
|---|---|---|---|---|---|---|---|
| | | IL-6 (pg/mL) | sTNFR1 (ng/mL) | sTNFR2 (ng/mL) | hsCRP (ng/mL) | sCD14 (ng/mL) | sCD163 (ng/mL) |
| **HIV status[2]** | WLHIV vs. WHIV- (ref.) | **0.63 (p=0.01)** | **0.58 (p<0.01)** | **-0.70 (p=0.01)** | -0.27 (p=0.20) | **0.34 (p<0.01)** | **0.29 (p<0.01)** |
| **Mode of HIV acquisition[3]** | PHIV vs. NPHIV (ref.) | 0.24 (p=0.44) | 0.33 (p=0.18) | 0.06 (p=0.86) | -0.33 (p=0.28) | 0.13 (p=0.12) | **0.19 (p=0.04)** |
| **ART regimen[4]** | ≥3 antiretroviral classes | -0.78 (p=0.04) | -0.35 (p=0.37) | -0.37 (p=0.38) | -0.59 (p=0.16) | 0.27 (p=0.06) | 0.19 (p=0.19) |
| | PI-based ART | 0.33 (p=0.31) | 0.23 (p=0.24) | 0.09 (p=0.77) | 0.02 (p=0.93) | 0.12 (p=0.14) | **0.19 (p=0.02)** |
| | NNRTI-based ART | 0.11 (p=0.71) | -0.10 (p=0.61) | -0.11 (p=0.68) | 0.11 (p=0.72) | 0.04 (p=0.63) | 0.13 (p=0.16) |
| | INSTI-based ART (ref.) | - | - | - | - | - | - |

[1]Estimated difference in adjusted mean log-transformed biomarker concentration between participants with the exposure of interest compared to those in the referent group.
[2]Adjusted for age at conception, race/ethnicity, education, gravidity, pre-pregnancy/1st trimester BMI, 1st trimester tobacco/alcohol/illicit drug use, any gonorrhea/chlamydia/trichomoniasis/syphilis/genital herpes during pregnancy.
[3]Adjusted for same covariates as [2], as well as HIV RNA level.
[4]Adjusted for same covariates as [2], as well as HIV RNA level and mode of HIV acquisition.

## 691 EPITOPES ASSOCIATED WITH ALTERED PATHOGENESIS IN VERTICAL HIV-1 TRANSMISSION

New Investigator Scholar

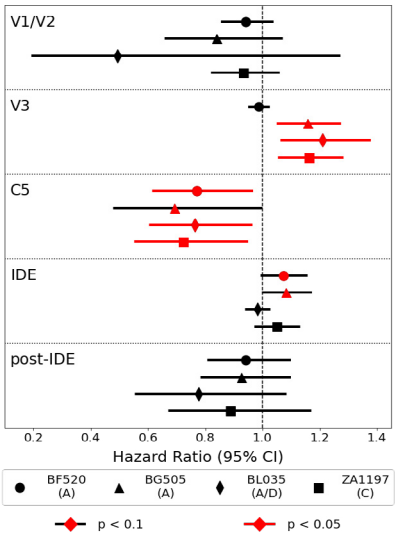
**Zak A. Yaffe**[1], Kevin Sung[1], Jared Galloway[1], Ruth Nduati[2], Frederick Matsen IV[1], Julie Overbaugh[1]
*[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]University of Nairobi, Nairobi, Kenya*

**Background:** Identifying correlates of protection from HIV acquisition and pathogenesis in humans is key to optimizing vaccine and prevention approaches. We studied the setting of breastfeeding mother to child transmission (MTCT) to determine whether passively-transferred antibodies (Abs) to specific Envelope (Env) epitopes are associated with HIV MTCT or pathogenesis.

**Methods:** Phage display of 1772 Env peptides from four HIV strains representing dominant clades in the cohort (3 subtype A and 1 subtype C) was used to map the epitope profile of passively-acquired Abs in plasma collected in the first week of life from 72 anti-retroviral naïve, breastfeeding infants from Nairobi, Kenya. We identified targeted Env regions using principal component analysis (PCA). To quantify the strength of Ab response to each region, we summed the enrichments of the corresponding peptides for each strain. Binomial logistic regression of enrichment and maternal viral load was used to determine whether regional responses were associated with HIV acquisition. Cox-proportional hazards models of infant survival were used to determine whether regional responses correlated with survival of infants that acquired HIV. A p-value less than 0.05 was considered significant.

**Results:** Responses to the V1/V2, V3, and C5 regions of gp120, as well as the immunodominant epitope (IDE) and post-IDE region for gp41 contributed high variance in PCA. Post-IDE enrichment was associated with reduced MTCT risk for the subtype C strain ($p = 0.020$), and there was also a trend for two subtype A strains ($p = 0.062$, $p = 0.060$), but not for the third ($p = 0.19$). Among the 21 infants that acquired HIV during the study (HIV+), responses to V3 and the IDE were associated with decreased survival in Cox-proportional hazards models (Figure 1). Conversely, responses to C5 were associated with increased survival of HIV+ infants.

**Conclusion:** Passively-acquired antibody responses targeting a post-IDE epitope were associated with reduced MTCT risk. For HIV+ infants, antibody responses to V3 loop or IDE were associated with decreased survival, whereas binding to the C5 region correlated with improved clinical outcome. The distinct contribution to disease outcome of Abs targeting different Env epitopes suggests that the pre-existing antibody repertoire can be both beneficial and detrimental to disease outcomes, depending on the epitope specificity of plasma Abs.




## 692 ASSOCIATION OF MATERNAL TDF-BASED ART WITH BONE MINERAL CONTENT IN BREASTFED INFANTS

**Tichaona Vhembo**[1], Kristin Baltrusaitis[2], Camlin Tierney[2], Maxensia Owor[3], Sufia Dadabhai[4], Avy Violari[5], Gerhard Theron[6], Dhayendre Moodley[7], Cynthia Mukwasi-Kahari[8], Kathleen George[9], John Shepherd[10], George K. Siberry[11], Renee Browning, Mary G. Fowler[13], Lynda Stranix-Chibanda[14]
*[1]University of Zimbabwe Clinical Trials Research Centre, Harare, Zimbabwe, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Makerere University–Johns Hopkins University, Kampala, Uganda, [4]Johns Hopkins Bloomberg School of Public Health, Blantyre, Malawi, [5]PHRU, University of the Witwatersrand, Johannesburg, South Africa, [6]Stellenbosch University, Cape Town, South Africa, [7]Center of the AIDS Programme of Research in South Africa and University of KwaZulu Natal, Durban, South Africa, [8]University of Zimbabwe Faculty of Medicine and Health Sciences, Harare, Zimbabwe, [9]FHI 360, Durham, NC, USA, [10]University of Hawaii Cancer Centre, Honolulu, HI, USA, [11]United States Agency for International Development, Washington, DC, USA, [12]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [13]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [14]University of Zimbabwe Faculty of Medicine and Health Sciences, UZ-CTRC, Harare, Zimbabwe*

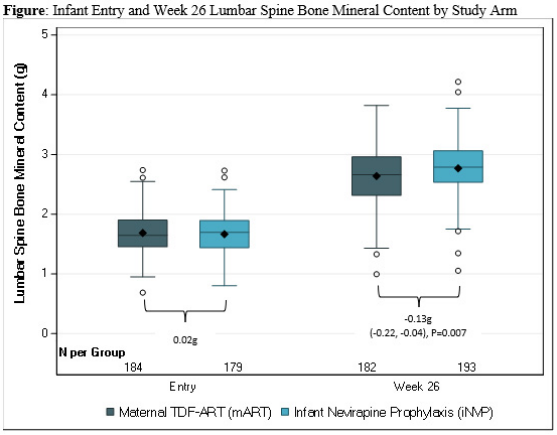
**Background:** Tenofovir disoproxil fumarate (TDF) is an important agent for antiretroviral treatment (ART) and prevention of HIV in breastfeeding women, but information about the impact of postpartum use on infant bone and renal safety is limited. The P1084s substudy assessed these outcomes in a subset of mother-infant (MI) pairs randomized to either maternal TDF-based ART [TDF/FTC+LPV/r] (mART) or infant nevirapine prophylaxis [no maternal ART] (iNVP) during breastfeeding as part of the IMPAACT PROMISE study.

**Methods:** Healthy MI pairs with normal maternal renal function and no antenatal exposure to maternal TDF who were randomized in PROMISE 1:1 to mART or iNVP at 6-14 days postpartum were eligible for the substudy. MI pairs were enrolled in P1084s on randomization day and followed through Week 74. Infant lumbar spine bone mineral content (LS-BMC) was assessed at entry and Week 26 by dual energy x-ray absorptiometry, read centrally by blinded investigators. Infant creatinine clearance (CrCl) was calculated using the revised Schwartz equation at entry and Weeks 10, 26, and 74. Student t-tests compared mean LS-BMC and CrCl at Week 26 and mean change from entry between arms. All differences are presented as mART – iNVP.

**Results:** 400 MI pairs were enrolled; 2 MI pairs in the mART arm were excluded because the mothers did not initiate TDF-ART. At entry, mean (standard deviation (sd)) infant LS-BMC was 1.68g (0.35) and CrCl was 64.2mL/min per 1.73 $m_2$ (24.6). At Week 26, 98% of MI pairs were breastfeeding and 96% were on their assigned antiretroviral strategy. Mean (sd) Week 26 LS-BMC was 2.64g (0.48) for mART and 2.77g (0.44) for iNVP; mean difference (95% confidence interval (CI)) -0.13g (-0.22, -0.04), P=0.007, n = 375/398 (94%) (Figure). Mean absolute (-0.14g (-0.23, -0.06)) and percent change (-10.88% (-18.53, -3.23)) in LS-BMC from entry was smaller for mART than iNVP. Similar results were observed in post hoc analyses of bone mineral density. At Week 26, mean (sd) CrCl was 130.0mL/min per 1.73 $m_2$ (34.9) for mART vs. 126.1mL/min per 1.73 $m_2$

(30.0) for iNVP; mean difference (95% CI) 3.8 (-3.0, 10.7), P = 0.27, n = 349/398 (88%). On average, CrCl increased from entry across all visits in both arms.
**Conclusion:** Although the mean LS-BMC at Week 26 was lower in breastfeeding infants with mART compared with iNVP, the difference was less than a half sd (~0.23g), thus clinical relevance is unlikely. No infant renal safety concerns were observed.

**Figure**: Infant Entry and Week 26 Lumbar Spine Bone Mineral Content by Study Arm




## 693 SIMILAR EARLY GROWTH IN HEU AND HUU INFANTS WITH MATERNAL ART OPTIMIZATION

**Maureen M. King'e**[1], Irene Njuguna[2], Christine J. McGrath[3], Michelle Bulterys[3], Hellen Moraa[4], Alvin Onyango[4], Sarah Benki-Nugent[3], Dalton C. Wamalwa[1], Grace John-Stewart[3]
*[1]University of Nairobi, Nairobi, Kenya, [2]Kenyatta National Hospital, Nairobi, Kenya, [3]University of Washington, Seattle, WA, USA, [4]University of Washington in Kenya, Nairobi, Kenya*

**Background:** While early growth differences between HIV exposed uninfected (HEU) and HIV unexposed uninfected infants (HUU) have been demonstrated, it is not known if these persist in the era of optimized maternal antiretroviral therapy (ART), including dolutegravir (DTG). We compared growth between HEU and HUU infants and evaluated the influence of maternal ART regimen, timing of ART initiation, and maternal viral load (VL) on growth in HEU infants.
**Methods:** HEU and HUU mother-infant pairs between the ages of 4 and 8 weeks were enrolled in 6 clinics in Nairobi and Kisumu, Kenya from March-September 2021. Continuous growth measures were calculated using WHO Z-scores (weight-for-age [WAZ], length-for-age [LAZ], weight-for-length [WLZ], head circumference-for-age [HCAZ]). Growth faltering was defined as underweight (WAZ<-2), stunting (HAZ<-2), wasting (HAZ<-2), and microcephaly (HCZ<-2). Linear regression models were used to compare continuous growth outcomes and Poisson regression to determine prevalence ratios (PR) and 95% confidence intervals (CI) for growth faltering outcomes.
**Results:** Of 1148 infants, 365 were HEU and 783 were HUU. Median age was 6 weeks (IQR: 6-7 weeks). HEU infants were more likely to be exclusively breastfed than HUU (Table 1). Women living with HIV (WLHIV) were older, had lower education, reported more moderate to severe household hunger and were underweight (BMI<18.5) compared to HIV-uninfected mothers. All WLHIV were on ART in pregnancy with 62% on DTG-based and 29% on Efavirenz-based regimens. Median duration on ART was 53 months (IQR: 16, 86 months). Most (85%) started ART pre-conception and 95% were virally suppressed in pregnancy. 97% of HEU were on ARV prophylaxis; 52% on NVP and 47% on AZT+NVP. HEU infants had similar LAZ, WAZ, WLZ, HCZ compared to HUU in unadjusted or adjusted models; there were no differences in prevalence of underweight, wasting, stunting, or microcephaly (p>0.05). Among HEU infants, there were no significant growth differences by timing of maternal ART initiation, regimen type, maternal VL or infant ARV prophylaxis.
**Conclusion:** HEU infants had similar growth in early infancy compared to HUU peers. Optimized maternal ART regimens and early ART initiation may result in similar early growth among HEU infants.

**Table 1.** Sociodemographic characteristics, growth Z-scores and prevalence of growth faltering between HEU and HUU infants at ages 4-8 weeks in Kenya.

| Characteristic | Overall, N = 1,148[1] n (%); Median (IQR) | HEU, N = 365[1] n (%); Median (IQR) | HUU, N = 783[1] n (%); Median (IQR) | Unadjusted Coeff (95% CI) | p-value | Adjusted[1] Coeff (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| Infant exclusively breastfed at 6 weeks | 1,107 (97%) | 363 (100%) | 744 (95%) | - | **<0.001** | - | - |
| Mother age (years) | 27.0 (24.0, 32.0) | 31.0 (26.0, 35.0) | 26.0 (23.0, 30.0) | - | **<0.001** | - | - |
| Mother education, primary or less | 395 (34%) | 170 (47%) | 225 (29%) | - | **<0.001** | - | - |
| Moderate to severe household hunger | 134 (12%) | **63 (17%)** | **71 (9%)** | - | **<0.001** | - | - |
| Mother BMI < 18.5kg | 31 (2.8%) | 17 (4.8%) | 14 (1.8%) | - | **0.005** | - | - |
| WAZ | 0.06 (2.70) | 0.13 (4.50) | 0.02 (1.12) | 0.11 [-0.23-0.45] | 0.52 | 0.15 [-0.21-0.51] | 0.41 |
| LAZ | -0.50 (2.21) | -0.55 (3.31) | -0.48 (1.44) | -0.07 **[-0.35-0.20]** | 0.61 | -0.05 [-0.34-0.24] | 0.75 |
| WLZ | 0.81 (4.15) | 1.10 (7.13) | 0.67 (1.25) | 0.43 [-0.09-0.95] | 0.11 | 0.50 [-0.05-1.05] | 0.07 |
| HCAZ | 0.88 (1.54) | 0.96 (1.19) | 0.84 (1.68) | 0.13 [-0.06-0.32] | 0.19 | 0.15 [-0.06-0.35] | 0.16 |

[1]Multivariate linear regression models for WAZ and WLZ adjusted for maternal age, maternal education, and infant sex; multivariate linear regression models for LAZ and HCAZ adjusted for maternal age, maternal height, and infant sex;
Abbreviations: CI, confidence interval; IQR, interquartile range

## 694 MATERNAL IPT IN PREGNANCY AND GROWTH FALTERING AMONG HIV-EXPOSED UNINFECTED INFANTS

**Ashenafi S. Cherkos**[1], Sylvia LaCourse[1], Daniel A. Enquobahrie[1], Grace Montepiedra[2], Carol Onyanog[3], Blandina T. Mmbaga[4], Tichaona Vhembo[5], Gaerolwe Masheto[6], Gerhard Theron[7], Adriana Weinberg[8], Amita Gupta[9], Grace John-Stewart[1] for the IMPAACT P1078 TB APPRISE Study team.
*[1]University of Washington, Seattle, WA, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Maasstad Hospital, Rotterdam, Netherlands, [4]Kilifi County Department of Health, Kilifi, Kenya, [5]University of Zimbabwe, Harare, Zimbabwe, [6]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [7]Tygerberg Hospital, Cape Town, South Africa, [8]University of Colorado Denver, Denver, CO, USA, [9]The Johns Hopkins University, Baltimore, MD, USA*

**Background:** Isoniazid preventive therapy (IPT) is recommended for pregnant women living with HIV. The TB APPRISE trial recently found that IPT initiation during pregnancy was associated with a significantly higher incidence of adverse pregnancy outcomes than postpartum IPT initiation. Effects of in utero IPT exposure on infant growth are unknown.
**Methods:** This post-hoc analysis used data from the TB APPRISE trial, a multicenter, double-blind, placebo-controlled, randomized clinical trial, in which mothers were randomized to a 28-week course of IPT starting during pregnancy or at postpartum week 12. Mother-infant pairs were followed to 48 weeks postpartum. Kaplan-Meier survival analysis and Cox proportional hazards regression were used to compare time to infant growth faltering (underweight: – weight-for-age z-score < -2, wasting: – weight-for-length < -2, or stunting: – length-for-age < -2) between arms to 12 weeks postpartum and to 48 weeks, and in sex-stratified analyses.
**Results:** Among 898 infants exposed to but without HIV (HEU) with growth data, median maternal age was 29 years (interquartile range: 24-33), 44723 (49.8%) were females, and 16557 (19.28.8%) were small for gestational age at birth. Baseline maternal and infant characteristics were similar between randomized arms. Six mothers and one infant developed TB during the study with similar TB rates between arms. Infants from pregnancy-IPT experienced 1.52-fold increased risk of being underweight in the first 12 weeks (95% CI:1.10, 2.11) and 1.36-fold increased risk of being underweight in the first 48 weeks (95% CI 1.03, 1.80). Pregnancy-IPT was not associated with wasting and stunting. In sex-stratified analyses, male infants in the pregnancy-IPT had 2.21-fold increased risk of being underweight (95% CI 1.40, 3.49) and 1.75 increased risk of being wasted (95% CI 1.13, 2.72) by 12 weeks postpartum and 1.88-fold increased risk of being underweight (95% CI 1.28, 2.77) and 1.47 increased risk of being wasted (95% CI 1.00, 2.16) by 48 weeks postpartum (Figure 1). There was no effect of maternal IPT timing in female infants.
**Conclusion:** In this post-hoc analysis, initiating IPT during pregnancy was associated with significantly increased risk of underweight among infants exposed to but without HIV in the first year of life. Male infants exposed to pregnancy-IPT had a significant risk of underweight and wasting over the first year of life. These data add to prior data from TB APPRISE, suggesting that IPT during pregnancy confers some risk to infants and that infant growth should be considered in risk-benefit evaluations of maternal IPT.

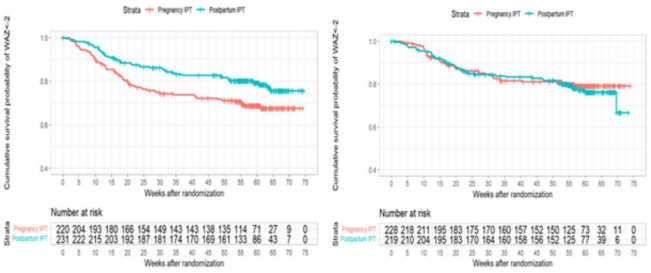



*Figure 1: Comparison of cumulative survival probability of underweight (defined as weight-for-age (WAZ)<-2) between male*

## 695 PREDICTORS OF NEURODEVELOPMENT IN HIV-EXPOSED–UNINFECTED INFANTS

**Michelle Bulterys**[1], Maureen M. King'e[2], Irene Njuguna[1], Daisy J. Chebet[2], Hellen Moraa[3], Jessica Dyer[1], Laurén Gomez[1], Melissa Gladstone[4], Christine J. McGrath[1], Anjuli D. Wagner[1], Dalton C. Wamalwa[2], Grace John-Stewart[1], Sarah Benki-Nugent[1]

*[1]University of Washington, Seattle, WA, USA, [2]University of Nairobi, Nairobi, Kenya, [3]Kenyatta National Hospital, Nairobi, Kenya, [4]University of Liverpool, Liverpool, UK*

**Background:** Over one million HIV-exposed uninfected (HEU) children are born annually in sub-Saharan Africa (SSA). Some but not all studies have found increased risk of neurodevelopmental delay, hospitalization, and mortality in HEU children compared to HIV-unexposed uninfected (HUU) children, but predictors of this association remain poorly understood.

**Methods:** Mothers living with and without HIV were recruited with their infants (HEU and HUU, respectively) at 4-10 weeks of age during routine postnatal care at 6 clinics in Kenya between March-October 2021. Infant neurodevelopment was assessed using the Malawi Developmental Assessment Tool (MDAT), a validated instrument that scores social, language, fine motor, and gross motor domains. Multivariate linear and log binomial regression models assessed associations between infant HIV and ART exposure and neurodevelopment scores, adjusting for confounders selected a priori.

**Results:** Compared to HUU infants (N=702), HEU infants (N=326) were slightly younger (6.2 vs. 6.4 weeks) and more likely to have an older mother with lower education and either unmarried or in a polygamous marriage. Among HEU infants, 50% received AZT+NVP regimens and 63% were exposed to maternal dolutegravir (DTG). Median maternal ART duration was 49.6 months (IQR: 13.3, 81.9), 87% of mothers were on ART pre-conception, and 95% of mothers were virally suppressed (VS) in pregnancy. Adjusting for infant age and sex, and maternal education and marital status, HEU and HUU infants had comparable MDAT scores in all four domains (Table 1). Among HEU infants, those receiving AZT+NVP regimens had significantly higher social and gross motor scores than those receiving NVP-alone ($p<0.05$). Furthermore, longer maternal ART duration was significantly associated with improved social and language scores ($p<0.05$). Maternal VS, pre-conception ART, and DTG use were not associated with differences in neurodevelopment scores.

**Conclusion:** In this cohort of HEU infants, with high frequency of maternal VS and DTG use, neurodevelopment at 6 weeks was comparable to HUU infants. The mechanism underlying higher neurodevelopment scores with maternal ART duration and infant combination ART is unclear and could reflect undetected differences in infant exposure to maternal virus or other factors. Longitudinal evaluation will be useful to discern biologic and sociocultural determinants of neurodevelopment among HEU infants.

**Table 1.** Comparing MDAT scores between HEU and HUU infants at age 6 weeks, and among HEU, identifying associations between infant and maternal ART characteristics and MDAT scores, adjusting for infant age and sex, and maternal education and marital status.

| | Social, Coeff or PR (95% CI) | P | Language, Coeff or PR (95% CI) | P | Fine Motor, Coeff or PR (95% CI) | P | Gross Motor, Coeff or PR (95% CI) | P |
|---|---|---|---|---|---|---|---|---|
| ***ENTIRE COHORT*** | | | | | | | | |
| ***HEU vs. HUU infants*** | | | | | | | | |
| HEU (ref: HUU) – Unadjusted | -0.12 [-0.24, 0.00] | **0.05** | 0.05 [-0.04, 0.16] | 0.28 | 0.00 [-0.15, 0.15] | 0.99 | -0.06 [-0.26, 0.14] | 0.55 |
| HEU (ref: HUU) – Adjusted [a] | -0.10 [-0.23, 0.03] | 0.12 | 0.06 [-0.04, 0.17] | 0.23 | 0.03 [-0.12, 0.18] | 0.72 | -0.05 [-0.25, 0.15] | 0.64 |
| ***HEU ONLY*** [b] | | | | | | | | |
| ***HEU Infant characteristics*** | | | | | | | | |
| Child is currently receiving AZT-based ART regimen (ref: NVP-alone) | **0.30 [0.09, 0.50]** | **<0.01** | -0.05 [-0.22, 0.12] | 0.54 | 0.14 [-0.23, 0.52] | 0.45 | **0.37 [0.02, 0.72]** | **0.04** |
| ***Maternal ART characteristics*** | | | | | | | | |
| Mother started ART post-conception (ref: pre-conception) | -0.16 [-0.46, 0.14] | 0.30 | -0.03 [-0.29, 0.22] | 0.80 | -0.44 [-0.97, 0.10] | 0.11 | 0.00 [-0.51, 0.52] | 0.99 |
| Duration on ART (months) | **0.01 [0.00, 0.01]** | **0.02** | **0.00 [0.00, 0.01]** | **0.04** | 0.00 [-0.00, 0.01] | 0.21 | -0.00 [-0.00, 0.00] | 0.70 |
| Most recent ART regimen received during pregnancy was non-DTG based (ref: DTG-based) | 0.04 [-0.18, 0.26] | 0.72 | -0.04 [-0.22, 0.15] | 0.69 | 0.10 [-0.30, 0.49] | 0.63 | -0.15 [-0.52, 0.22] | 0.42 |
| Mother is virally unsuppressed at 400 copies/ml (ref: suppressed) | 0.11 [-0.51, 0.73] | 0.73 | -0.29 [-0.82, 0.26] | 0.30 | -0.03 [-1.29, 1.22] | 0.96 | 0.47 [-0.61, 1.54] | 0.39 |

[a] Multivariate linear regression models adjusted for infant age and sex, and maternal education and marital status.
[b] Multivariate linear regression models adjusted for infant age and sex.

## 696 MITOCHONDRIAL PROTON LEAK IN INFANTS WITH IN UTERO HIV AND ART EXPOSURE IN BOTSWANA

**Jennifer Jao[1],** Shan Sun[2], Lauren C. Balmert[1], Justine Legbedze[2], Keolebogile N. Mmasa[3], Gosego N. Masasa[3], Samuel N. Kgole[3], Sikhulile Moyo[3], Joseph Makhema[3], Mitchell E. Geffner[4], Elaine J. Abrams[5], Irwin J. Kurland[6], Anastasia Andrukhiv[7], Kathleen M. Powis[8], Mariana Gerschenson[7]

*[1]Northwestern University, Chicago, IL, USA, [2]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA, [3]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [4]University of Southern California, Los Angeles, CA, USA, [5]ICAP at Columbia University, New York, NY, USA, [6]Albert Einstein College of Medicine, Bronx, NY, USA, [7]University of Hawaii at Manoa, Honolulu, HI, USA, [8]Massachusetts General Hospital, Boston, MA, USA*

**Background:** There are limited data on mitochondrial (mt) function in infants HIV-uninfected with in utero HIV and current antiretroviral therapy (ART) exposure (HEU).

**Methods:** Infants HEU and infants HIV-unexposed uninfected (HUU) were enrolled in the Tshilo Dikotla study in Botswana from 2016-2019. Mt basal and maximal respiration, ATP production, proton leak, spare respiratory capacity, and non-mt respiration were measured using a Seahorse XFe96 in viable peripheral blood mononuclear cells from infants at 1 month (mo) of age. Data on socio-demographics, maternal body mass index (BMI), gestational diabetes (GDM), HIV disease, and ART history, as well as infant preterm birth (<37 weeks gestation), breastfeeding, anthropometrics, and Homeostatic Model Assessment – Insulin Resistance (HOMA) were collected. Z scores for weight (WAZ) and length (LAZ) were calculated. Linear regression models were fit to assess the association between in utero HIV/ART exposure and each log-transformed mt function parameter, adjusting for confounders. Subgroup analyses were performed in infants HEU to assess the association of in utero ART [tenofovir (TDF)/emtricitabine (FTC)/dolutegravir (DTG) vs. TDF/FTC/efavirenz (EFV)] with each mt outcome.

**Results:** Of 202 infants, 133 were HEU. Maternal age (29 vs. 26 yr, $p<0.01$) and parity (3 vs. 1, $p<0.01$) were higher among women of infants HEU vs HUU. Family history of DM, annual income, maternal BMI, GDM, tobacco/alcohol/substance use, preterm birth, and infant WAZ and LAZ were similar between groups. Among mothers of infants HEU, 47% had a CD4 count >500 cells/$mm_3$ and 93% a viral load <40 copies/mL at enrollment, 68% received TDF/FTC/DTG, and 32% TDF/FTC/EFV. Median levels of mt proton leak were higher in infants HEU vs HUU [12.45 vs 10.78 pmol/min, $p=0.02$] in univariate analysis. (Table) This relationship persisted even after adjusting for maternal age, GDM, infant sex, preterm birth, WAZ, breastfeeding, and HOMA (mean difference in proton leak was 0.15 log units higher in HEU vs HUU, $p<0.01$). No differences in any other mt parameters were noted between groups. Among infants HEU, there was no association of in utero ART with any mt parameter.

**Conclusion:** In this cohort, infants HEU had higher mt proton leak compared to infants HUU at 1 mo of age, indicating immune cell mt uncoupling. While mt uncoupling may be a compensatory mechanism, it is also associated with increased oxidative stress which could potentially lead to metabolic diseases. Future studies are needed.

Table. Mitochondrial Oxygen Consumption Rate (OCR) Measures by HIV/ART Exposure Status

| | HEU infants (n=133) (pmol/min) | HUU infants (n=69) (pmol/min) | *p*-value |
|---|---|---|---|
| Basal respiration | 45.66 (32.82 - 63.94) | 47.16 (30.96 - 60.52) | 0.40 |
| Maximal respiration | 121.60 (86.68 - 176.30) | 118.20 (71.49 - 155.90) | 0.18 |
| ATP production | 33.01 (23.72 - 47.77) | 36.35 (21.57 - 50.46) | 0.45 |
| Proton leak | 12.45 (8.35 - 16.95) | 10.78 (6.43 - 14.59) | 0.02 |
| Spare respiratory capacity | 73.71 (45.48 - 113.6) | 62.77 (35.49 - 103.7) | 0.10 |
| Non-mitochondrial respiration | 22.07 (13.41 - 27.83) | 19.56 (13.20 - 27.45) | 0.20 |

*All values expressed as median (interquartile range) area-under-the-curve units. P values from Wilcoxon tests. ART=antiretroviral therapy; ATP=adenosine triphosphate, HEU=HIV-exposed uninfected, HUU=HIV-unexposed uninfected*

## 697 HEARING LOSS AND FETAL EXPOSURE TO ANTIRETROVIRAL DRUGS IN HIV-UNINFECTED CHILDREN

**Peter Torre**[1], Zhongli Zhang[2], Toinette Frederick[3], Murli Purswani[4], Howard J. Hoffman[5], Paige L. Williams[2], Tzy-Jyun Yao[2]
*[1]San Diego State University, San Diego, CA, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University of Southern California, Los Angeles, CA, USA, [4]Bronx-Lebanon Hospital Center, Bronx, NY, USA, [5]National Institutes of Health, Bethesda, MD, USA*

**Background:** Early identification of hearing loss is needed to allow for interventions that can minimize subsequent adverse effects on speech and language development, academic performance, and social interactions. Little is known about hearing sensitivity following fetal exposure to maternal antiretroviral (ARV) drugs among children who remain HIV-uninfected.
**Methods:** We included all 5-year-old children who were HIV-exposed but uninfected (CHEU) enrolled in the Surveillance Monitoring for ART Toxicities (SMARTT) cohort of the Pediatric HIV/AIDS Cohort Study (PHACS) with valid middle ear and pure-tone threshold data from an audiometric examination after August 2010. A pure-tone average (PTA), defined as the mean of air-conduction thresholds in decibels (dB) over frequencies of 0.5, 1, 2, and 4 kHz, was calculated for each ear. Hearing loss was defined as a worse-ear PTA>15 dB. Log-binomial models were fit using generalized estimating equations to assess the association between fetal ARV exposure and hearing loss, stratified by timing of fetal ARV exposure, either from conception versus after conception.
**Results:** Of 1265 CHEU with audiometric exams, 1081 CHEU had valid pure-tone data (49% female; mean age=5.16 [SD=0.25] years, 64% Black, and 35% Hispanic). The overall prevalence of hearing loss was 15%, including 15% among those exposed from conception, and 12%, 15%, and 20% among those with 1st, 2nd, and 3rd trimester of initial ARV exposure, respectively. Over 80% of hearing loss was sensorineural, regardless of timing of first ARV exposure. A majority of CHEU (83%) were exposed to regimens containing zidovudine/lamivudine (ZDV/3TC) without atazanavir/ritonavir [ATV/r]) or tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) with or without ATV/r. No strong evidence of an association between ARV exposure and hearing loss was found for those first exposed to ARVs at conception. For CHEU with first ARV exposure after conception, regimens containing ZDV/3TC were associated with a higher risk for hearing loss (RR=1.57, 95% CI=1.01-2.44) compared to regimens containing TDF/FTC (Table).
**Conclusion:** CHEU had an overall hearing loss prevalence of 15%. For those first exposed to ARVs after conception, prevalence increased over trimester of first exposure. TDF/FTC containing regimens, relative to ZDV/3TC containing regimens, may be protective. Further research is warranted to better understand the contribution of ARVs and other factors to hearing loss in CHEU.

Table: Relative risk of hearing loss associated with fetal exposure to regimens containing ZDV/3TC without ATV/r, TDF/FTC without ATV/r or TDF/FTC with ATV/r, stratified by timing of first ARV exposure.

| | Unadjusted[a] | | | Adjusted[a,b] | | |
|---|---|---|---|---|---|---|
| **Exposure started from conception** | RR | 95% CI | *p* value | RR | 95% CI | *p* value |
| TDF/FTC, without ATV/r (N=170, 16%[c]) | Ref | | | | | |
| TDF/FTC, with ATV/r (N=85, 18%[c]) | 1.10 | (0.62, 1.96) | 0.74 | 1.10 | (0.63, 1.89) | 0.74 |
| ZDV/3TC, without ATV/r (N=111, 11%[c]) | 0.69 | (0.36, 1.33) | 0.27 | 0.70 | (0.37, 1.31) | 0.26 |
| | | | | | | |
| **Exposure started after conception** | RR | 95% CI | *p* value | RR | 95% CI | *p* value |
| TDF/FTC, without ATV/r (N=88, 10%[c]) | Ref | | | | | |
| TDF/FTC, with ATV/r (N=84, 12%[c]) | 1.16 | (0.75, 1.79) | 0.50 | 1.03 | (0.67, 1.59) | 0.88 |
| ZDV/3TC, without ATV/r (N=359, 16%[c]) | 1.57 | (0.88, 2.79) | 0.13 | 1.57 | (1.01, 2.44) | 0.04 |

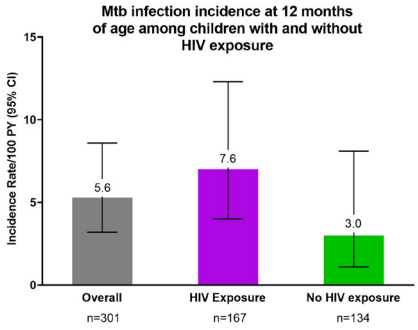
RR: relative risk; CI: confidence interval; ZDV/3TC: zidovudine and lamivudine; TDF/FTC: tenofovir disoproxil fumarate and emtricitabine; ATV/r: atazanavir with or without ritonavir booster; ARV: antiretroviral

[a]: Models were fit among children with valid pure-tone data for left or right ear, with fetal exposure to (1) ZDV/3TC without ATV/r, (2) TDF/FTC without ATV/r, or (3) TDF/FTC with ATV/r. All three groups could have included exposure to other protease inhibitors, non-nucleoside reverse transcriptase inhibitors, or integrase strand transfer inhibitors. Separate models were fit for children whose mothers were on ART from conception and those whose mothers initiated ART after conception.
[b]: adjusted for years of age at audiometric examination, sex, race, and Hispanic ethnicity.
[c]: % of hearing loss

## 698 Mtb INFECTION IN CHILDREN WITH AND WITHOUT HIV-EXPOSURE IN THE FIRST YEAR OF LIFE

**Sylvia LaCourse**[1], Jerphason O. Mecha[2], Jaclyn Escudero[1], Barbra A. Richardson[1], Elizabeth Maleche-Obimbo[3], Daniel Matemo[2], John Kinuthia[2], Grace John-Stewart[1]
*[1]University of Washington, Seattle, WA, USA, [2]Kenyatta National Hospital, Nairobi, Kenya, [3]University of Nairobi, Nairobi, Kenya*

**Background:** Young children, including those with maternal HIV exposure, are at increased risk of active tuberculosis (TB). Estimates of M. tuberculosis (Mtb) infection in the first year of life in the contemporary setting of widespread community antiretroviral therapy (ART) uptake and isoniazid preventive therapy (IPT) are limited.
**Methods:** Pregnant women with and without HIV and their children were enrolled in a longitudinal cohort study in western Kenya. Mtb infection was assessed in mothers in pregnancy with interferon gamma-release assay (QFT-Plus) and tuberculin skin test (TST; HIV+ TST ≥5 mm and HIV- TST ≥10 mm considered positive); children underwent TST at 12 months (with same TST cut-offs used). We estimated infant incident Mtb infection (TST positivity) at 12 months and assessed correlates of infant Mtb infection using generalized linear models.
**Results:** Among 301 infants with 12-month TST results, 167 (55%) were HIV-exposed (including 2 with subsequent HIV diagnosis at 6 weeks and 6 months of age) and 134 (45%) were HIV-unexposed, 155 were female (51.5%), and most received BCG vaccination (299, 99%). Median maternal age was 26 years (IQR 22-30). Among 167 infants with HIV exposure, all mothers were on ART at enrollment and 133 (80%) had received IPT of whom 31 (23%) were on IPT during enrollment in pregnancy. Overall, 17/301 (5.7%) infants had a positive TST for a cumulative Mtb infection incidence of 5.6/100 PY (95%CI 3.5-9.0)/100 PY at 12 months. Mtb infection prevalence was 7.8% (13/167) among children with HIV exposure (including 1 child with HIV) and 3.0% (4/134) among children without HIV exposure (7.6 vs. 3.0/100PY, HR 2.5 [95%CI 0.8-7.8], p=0.10). Among children with HIV exposure, Mtb infection prevalence was similar with (7.7%) and without maternal IPT use (7.9%) (7.6 vs. 7.5/100PY, HR 1.0 [95%CI 0.3-3.0], p=0.99). Infant Mtb infection was associated with maternal TST positivity (RR 2.9 [95%CI 1.1-7.7], p=0.04), but not QFT-Plus positivity (RR 1.4 [95%CI 0.6-3.6], p=0.46).
**Conclusion:** Infant latent TB infection incidence (as measured by TST) at 12 months of age was approximately 2.5-fold higher among children born to mothers with HIV, though not statistically significant, despite high levels of maternal isoniazid preventive therapy.




## 699 IDENTIFYING HIV-POSITIVE MOTHERS AND EXPOSED INFANTS IN MATERNAL CHILD SERVICES

**Chloe A. Teasdale**[1], Michelle Choy[2], Fatima Tsiouris[2], Eduarda Pimental de Gusmao[3], Etelvino Banqueiro[3], Nicole Flowers[4], Marilena Urso[5], Mirriah Vitale[3], Elaine J. Abrams[2]
*[1]CUNY Graduate School of Public Health and Health Policy, New York, NY, USA, [2]ICAP at Columbia University, New York, NY, USA, [3]ICAP at Columbia University, Maputo City, Mozambique, [4]Centers for Disease Control and Prevention, Atlanta, GA, USA, [5]US Centers for Disease Control and Prevention, Maputo, Mozambique*

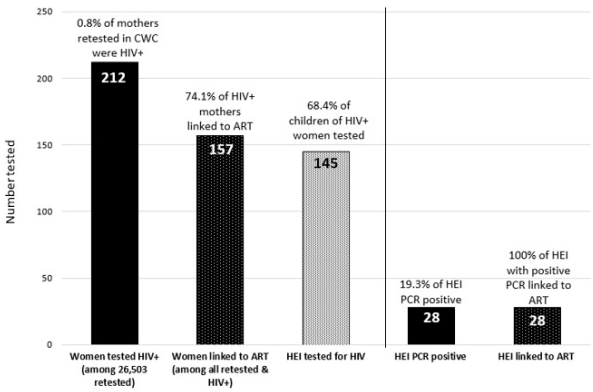
**Background:** HIV retesting for women who previously tested HIV-negative or who were not tested during pregnancy and delivery is critical for identifying women living with HIV and initiating them on ART. Retesting also identifies infants at risk for HIV infection who need linkage to care.
**Methods:** In collaboration with the Mozambican Ministry of Health and the CDC, ICAP at Columbia University provided technical assistance to expand HIV

retesting for mothers in maternal child health services (MCH) at 10 health facilities in Nampula, Mozambique from April through November 2019. The project was conducted in child wellness and immunization clinics (CWC). Retesting procedures followed national HIV guidelines which called for testing every 3 months during breastfeeding. To identify women eligible for retesting, health facility staff examined patient held health cards for date of last HIV test. Two additional HIV test counselors and one mentor mother were hired to identify eligible women and support testing at each health facility for the project. Routinely collected data were extracted from health facility registers for evaluation. We report the number and proportion of women: retested in CWC; tested HIV-positive; linked to ART services; and the number HIV-exposed infants (HEI) tested for HIV (with polymerase chain reaction (PCR) testing); HEI testing HIV+; HIV+ HEI linked to ART services. We also report HIV test positivity for mothers according to the age of their infants in months.

**Results:** A total of 26,503 women were tested for HIV in the CWC over 8 months; 212 (0.8%) tested HIV+ and 157 (74.1%) of those testing HIV+ were linked to ART services. Among HEI identified as a result of maternal HIV testing in CWC, 145 (68.4%) received PCR testing and 28 (19.3%) tested positive. All HEI (100%) with positive PCR were linked to ART services. Maternal test positivity in the CWC was 1.1% in infants 1-4 months of age. Maternal test positivity was lowest (0.6%) among mothers of infants 5 months of age and highest (1.6%) in mothers of children >12 months of age.

**Conclusion:** Testing yield for mothers was low in CWC services, linkage to infant testing was poor and 19.3% of infants of women who tested HIV+ were found to have HIV infection. Given the challenges of retesting large numbers of women attending MCH services, effective methods for targeting testing in these settings will help identify more HIV+ women and their infants.

**Figure 1. Maternal retesting, HIV-exposed infant testing and linkage to ART in Child Welfare Clinics (CWC), Nampula, Mozambique April-November 2019**




## 700 EVALUATION OF CAB-LA SAFETY AND PK IN PREGNANT WOMEN IN THE BLINDED PHASE OF HPTN 084

Late Breaking

**Sinead Delany-Moretlwe[1],** James Hughes[2], Xu Guo[3], Brett Hanscom[3], Craig W. Hendrix[4], Jennifer Farrior[5], Rebecca H. Berhanu[6], Alex R. Rinehart7, Susan L.Ford[7], James F. Rooney[8], Adeola Adeyeye[9], Raphael J. Landovitz[10], Myron S. Cohen[11], Mina C. Hosseinipour[11], Mark Marzinke[4]

*[1]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [2]University of Washington, Seattle, WA, USA, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]FHI 360, Durham, NC, USA, [6]Boston University School of Public Health, Boston, MA, USA, [7]ViiV Healthcare, Research Triangle Park, NC, USA, [8]Gilead Sciences, Inc, Foster City, CA, USA, [9]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [10]University of California Los Angeles, Los Angeles, CA, USA, [11]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** HPTN 084 is a Phase III randomized, double-blind, double-dummy trial that showed that long-acting injectable cabotegravir (CAB-LA) was superior to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in preventing HIV in women in sub-Saharan Africa. Participants were required to use long-acting contraception; however, pregnancies occurred during the trial. We report on the safety and pharmacokinetics of CAB-LA in women who became pregnant in HPTN 084.

**Methods:** If a participant had a confirmed pregnancy, study injections were withheld and she was offered open-label TDF/FTC through pregnancy outcome and until cessation of breastfeeding, unblinded to study arm, and continued follow-up visits; live infants were assessed at birth and 12 months. Adverse events (AE) post-confirmation of pregnancy were compared between study arms. The apparent terminal phase half-life ($t_{1/2}$app) of CAB-LA in pregnant women in HPTN 084 was compared to non-pregnant women from HPTN 077, a Phase II safety and pharmacokinetics study.

**Results:** There were 49 confirmed pregnancies (29 CAB, 20 TDF/FTC) in 48 participants during the blinded phase of the study. Pregnancy incidence was 1.3 per 100 person-years (py). CAB-LA participants (n=6) experienced more pregnancy-related AE, including premature rupture of membranes (n=2), pre-eclampsia (n=1), oligohydramnios (n=1), incomplete abortion (n=1) and morning sickness (n=1) than TDF/FTC participants (morning sickness n=1). None of these AE were considered as product-related. No congenital anomalies were observed. Of the 43 participants (26 CAB-LA, 17 TDF/FTC) with confirmed pregnancy who received at least one injection, the incidence of ≥ grade 2 AEs in the CAB arm was 113/100 py (95% CI: 69.3-185.4/100 py) vs. 166/100 py (95% CI: 102.2-271.0/100 py) in the TDF/FTC arm (p=0.064). The CAB $t_{1/2}$app geometric mean was 62.0 days (95% CI 43.7-88.0) for HPTN 084 pregnant women as compared to 64.3 days (95% CI: 51.1-80.8) in HPTN 077 non-pregnant women. Age, weight, race, and pregnancy status were not significantly associated with $t_{1/2}$app. Body mass index (BMI) >27.2 kg/$m_2$ was associated with a longer CAB $t_{1/2}$app (fold-change: 1.49, 95% CI: 0.97-2.28; p=0.069).

**Conclusion:** Residual CAB-LA was generally well tolerated in pregnant women. The $t_{1/2}$app was comparable between pregnant and non-pregnant women. Ongoing studies will examine the safety and pharmacology of CAB-LA in women who choose to continue CAB-LA through pregnan

## 701 RECENT HIV INFECTION AMONG PREGNANT WOMEN FROM 2 NATIONAL SURVEYS IN SOUTH AFRICA

**Selamawit A. Woldesenbet[1]**, Mireille Cheyip[2], Tendesayi Kufa-Chakezha[1], Carl Lombard[3], Samuel Manda[4], Kassahun Ayalew[2], Adrian Puren[1]

*[1]National Institute for Communicable Diseases, Johannesburg, South Africa, [2]US Centers for Disease Control and Prevention Pretoria, Pretoria, South Africa, [3]South African Medical Research Council, Cape Town, South Africa, [4]South African Medical Research Council, Pretoria, South Africa*

**Background:** Incident HIV infection among pregnant women contributes up to 25% of vertical HIV transmissions in Sub-Saharan African countries. UNAIDS aimed to reduce HIV incidence by 75% by 2020. Among pregnant women in South Africa, this is equivalent to reducing HIV incidence to <1%. Recent infection testing algorithms (RITA) can be used to monitor trends in incident HIV infection and meaningfully evaluate the performance of HIV programs. We assessed progress towards the UNAIDS target among pregnant women in South Africa using nationally representative surveys.

**Methods:** Data were obtained from two cross-sectional antenatal sentinel surveys conducted in South Africa in 2017 and 2019. In each survey, about 36,000 pregnant women aged 15-49 years old attending antenatal care in 1590 public health facilities were enrolled. Blood specimens were collected from each pregnant woman and tested for HIV. Plasma viral load and limiting-antigen avidity (LAg) assay tests were performed on HIV-positive specimens. Socio-demographic and other health data were collected by interview. A RITA that combined a LAg assay and viral load information was applied to distinguish recent (≤1 year) infections from long-term infections (>1 year). The calculated proportion of HIV-positive women with recent infection was adjusted for assay-specific parameters to estimate annualized HIV incidence. The outcome variable, HIV infection duration was multiclass (recent infection, long-term infection and HIV-negative). This was modelled using a multinomial logistic regression (using HIV-negative group as a reference), accounting for the survey design.

**Results:** Of 10,049 and 10,688 HIV-positive participants with LAg and viral load data in 2017 and 2019 respectively,1.4%(136) and 1.3%(140) were recently infected. The annual HIV incidence was 1.5% (95% confidence interval (CI): 1.2–1.7) and 1.2% (95%CI: 1.0–1.4) in 2017 and 2019, respectively. Being in a non-marital or age-disparate relationship, residing in a rural area, having high school education or lower, and current pregnancy that was unintended or from a multigravida woman were significantly associated with higher odds of recent infection.

**Conclusion:** Across both years, incidence fell short of the UNAIDS target. Interventions to reduce incident infections in South Africa could target high-risk groups identified in this study and integrate messages of dual protection of

HIV and unintended pregnancy. Continued surveillance is vital for monitoring incidence trends and program performance.

## 702 HIV TEST-POSITIVITY IN PREGNANT AND POSTNATAL WOMEN RETESTED IN NAMPULA, MOZAMBIQUE

**Chloe A. Teasdale**[1], Michelle Choy[2], Fatima Tsiouris[2], Eduarda Pimental de Gusmao[3], Etelvino Banqueiro[3], Nicole Flowers[4], Marilena Urso[5], Mirriah Vitale[3], Elaine J. Abrams[2]

*[1]CUNY Graduate School of Public Health and Health Policy, New York, NY, USA, [2]ICAP at Columbia University, New York, NY, USA, [3]ICAP at Columbia University, Maputo City, Mozambique, [4]Centers for Disease Control and Prevention, Atlanta, GA, USA, [5]US Centers for Disease Control and Prevention, Maputo, Mozambique*

**Background:** Identifying pregnant women living with HIV and initiating them on ART is critical for maintaining their health and decreasing vertical transmission risk. Repeat testing during pregnancy and the postnatal (PN) period is important for finding women with incident infections and those already living with HIV who have been lost to care.

**Methods:** ICAP at Columbia University, in collaboration with Mozambique's Ministry of Health and the CDC, conducted a technical assistance project to support implementation of national HIV testing guidelines for pregnant and postnatal women at 10 health facilities in Nampula, Mozambique, from April-November 2019. We provided technical assistance in 5 service areas: antenatal care (ANC), maternity, PN, family planning (FP) and child wellness clinics (CWC), which included clinical mentorship, identification of retesting gaps and allocation of additional staff (CWC only). Routinely collected data were extracted from health facility registers. From ANC, we report numbers and proportions of women: eligible for retesting in ANC; returned for care when retesting eligible (>3 months after first test); retested; and HIV-positive (HIV+) at retesting. For other services, we report test positivity (proportion of HIV+ among all tested) overall and by age group.

**Results:** In ANC, 28,233 pregnant women tested HIV-negative at first ANC visit and 11,504 (40.7%) had a follow-up ANC visit when retesting eligible. Among pregnant women who returned, 84.8% were retested and 26 (0.3%) tested HIV+. Among 4,468 women retested in maternity, 1.2% were HIV+; in 697 women retested in PN clinics, 1.0% were HIV+; among 678 women retested in FP clinics, 2.1% were HIV+; and in 39,499 women retested in CWC, 1.0% were HIV+ (Table 1). Women 10-14 years had the highest test-positivity of all age groups in maternity (10.3%) and PN clinics (16.7%). Test positivity was similar for women 15-19 years across all settings (0.7% - 1.1%) and highest for women 30-34 years in FP clinics (3.6%). Few women 40+ years tested HIV+.

**Conclusion:** Less than half of pregnant women eligible for retesting in ANC returned for follow-up visits during pregnancy but testing uptake among returners was high and HIV positivity was low. Adolescents in maternity wards and PNC had the highest test positivity while older women attending FP clinics also had high positivity. These data underscore the importance of retesting for pregnant and postnatal women and identifying key venues and priority groups for targeted HIV retesting.

**Table 1. Women retested in maternity, postnatal, family planning and child wellness clinics and proportion HIV-positive by age, Nampula, Mozambique, April-November 2019**

| | All women | Maternal age (years) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 10-14 | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40+ |
| **Maternity (labor & delivery)** | | | | | | | | |
| Women retested | 4,468 | 39 | 1,280 | 1,408 | 947 | 530 | 215 | 49 |
| Percent HIV-positive | 1.2% | 10.3% | 1.1% | 1.2% | 1.0% | 1.1% | 0.9% | 0.0% |
| **Postnatal clinic** | | | | | | | | |
| Women retested | 697 | 18 | 221 | 240 | 127 | 50 | 37 | 4 |
| Percent HIV-positive | 1.0% | 16.7% | 1.4% | 0.0% | 0.0% | 2.0% | 0.0% | 0.0% |
| **Family planning clinic** | | | | | | | | |
| Women retested | 678 | 1 | 137 | 253 | 196 | 56 | 23 | 12 |
| Percent HIV-positive | 2.1% | 0.0% | 1.5% | 3.2% | 1.0% | 3.6% | 0.0% | 0.0% |
| **Child wellness clinics** | | | | | | | | |
| Women retested | 39,499 | 160 | 11,096 | 13,257 | 7,780 | 4,193 | 2,116 | 897 |
| Percent HIV-positive | 1.0% | 1.3% | 0.7% | 1.0% | 1.3% | 1.2% | 1.1% | 0.3% |

## 703 PREGNANCY IN WOMEN WITH HIV IN A TUBERCULOSIS-PREVENTIVE THERAPY TRIAL

New Investigator Scholar

**Priya Singh**[1], Lawrence Moulton[2], Grace Link Barnes[1], Amita Gupta[1], Reginah Msandiwa[3], Richard E. Chaisson[1], Neil A. Martinson[3]

*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]Perinatal HIV Research Unit, Soweto, South Africa*

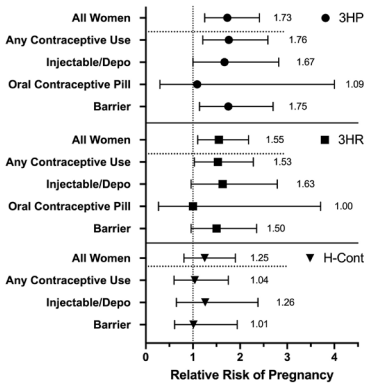
**Background:** Tuberculosis (TB) during pregnancy in women with HIV infection is associated with both poor maternal and child outcomes. TB preventive therapy (TPT) is recommended for people with HIV infection, including during pregnancy. However, the impact of TPT exposure at conception and during pregnancy is poorly documented.

**Methods:** We report pregnancy outcomes among South African women with HIV and a positive tuberculin skin test who were enrolled in a large single center, open-label randomized trial of 4 TPT regimens (rifapentine/isoniazid for 3 months [3HP], rifampin/isoniazid for 3 months [3HR], isoniazid for 6 months [6H] and continuous isoniazid [HCont]) before universal antiretroviral therapy was recommended in South Africa. Women who conceived were offered continuation of preventive treatment with isoniazid for six months. Descriptive statistics and risk ratios were assessed to examine relationships between study regimens, incident pregnancy, contraceptive use, and adverse pregnancy outcomes (abortion, preterm birth, neonatal death).

**Results:** Of 896 women enrolled, 216 (24%) conceived during the study. Women who conceived were younger (27.9 vs 31.3 years, $p < 0.001$) and had higher mean baseline CD4 counts (589.1 vs 536.7, $p = 0.011$) than women who did not. The odds of pregnancy were higher in women in the rifamycin-containing arms than the two isoniazid arms (3HP: 1.73, $p = 0.001$; 3HR: 1.55, $p = 0.017$); despite these arms being associated with increased contraceptive use compared to the standard 6H therapy (3HP: 1.76, $p = 0.004$; 3HR: 1.53, $p = 0.04$). When stratified by contraceptive types, barrier contraceptive use was associated with an increased pregnancy risk, especially in the 3HP arm (1.75, $p = 0.012$). Pregnancy occurred in 34 (16%) women while they were taking preventive treatment (8 rifamycin, 26 isoniazid monotherapy). Pregnancy outcomes in those who conceived on TBT were: 17 (50%) mother/baby healthy, 3 (9%) spontaneous abortions, 6 (18%) elective abortions, 1 (3%) premature delivery, 2 (6%) neonatal deaths [1 rifamycin and 1 isoniazid], and 5 (15%) outcomes were unknown. No women who became pregnant subsequently developed TB.

**Conclusion:** Pregnancy was common in women receiving TPT and was more frequent in women who received rifamycin-based regimens.

**Figure 1. Pregnancy Risk Stratified by Treatment Arm**




## 704 PrEP CONTINUATION AND OBJECTIVE ADHERENCE IN PREGNANT/POSTPARTUM SOUTH AFRICAN WOMEN

**Dvora Joseph Davey**[1], Dorothy C. Nyemba[2], Rufaro Mvududu[2], Nyiko Mashele[2], Linda-Gail Bekker[3], Pamina M. Gorbach[1], Thomas J. Coates[1], Lubbe Wiesner[2], Jennifer Norman[2], Landon Myer[2]

*[1]University of California Los Angeles, Los Angeles, CA, USA, [2]University of Cape Town, Cape Town, South Africa, [3]Desmond Tutu HIV Foundation, Cape Town, South Africa*

**Background:** Effective oral pre-exposure prophylaxis (PrEP) requires daily adherence but little is known about objective levels of adherence during pregnancy and postpartum.

**Methods:** We enrolled consenting pregnant, HIV-uninfected cisgender women at first antenatal care (ANC) visit with follow-up through 12-months postpartum. Women and girls >15-yrs who were eligible for the study received HIV prevention counseling and were offered PrEP. We analyzed the proportion of women who continued on PrEP after 3-months and objective levels of adherence using an indirect liquid chromatography with tandem mass spectrometry dried blood spot (DBS) tenofovir diphosphate (TDF-DP) assay. We evaluated TDF-DP levels stratified by pregnancy vs. postpartum with associated correlates in women taking PrEP by estimating the prevalence ratios adjusting for age and relationship status.

**Results:** Between August 2019 and October 2021, we enrolled 1201 pregnant women (median age=26 years; median gestation=21 weeks). Following PrEP counseling, 84% of women initiated PrEP at their first ANC visit (n=1014); 55% were married or cohabiting. At 1-month, 66% of women on PrEP returned for a repeat prescription and 58% returned at 3-months. We analyzed DBS in women who returned at 3-months and reported any PrEP use in past month (n=179 of 229 returning for 3m visit [78%]). Two-thirds (65%) had TDF-DP present in their blood (n=117 of 179); 73% in postpartum and 62% in pregnancy (p=0.20). Over half of women (52%; n=94) took PrEP <7 days per week, indicating that many women used PrEP intermittently and not daily, with most (35%; n=63) taking PrEP <2-times in the past week. Overall, 14% of pregnant women (n=19 of 84), and 9% of postpartum women (n=4 of 45) had TDF-DP levels consistent with taking PrEP 7 days per week (p=0.52; Table 1). Correlates of having TDF present in blood were older maternal age (24+ yrs old; adjusted prevalence ratio [aPR]=1.10; 95% CI=0.97, 1.25), early gestational age at first ANC visit (aPR=1.10; 95% CI=1.00, 1.01), single relationship status vs. married/cohabiting (aPR=1.14; 95% CI=0.98, 1.32), and high baseline HIV risk perception (aPR=1.39; 95% CI=1.10, 1.52).

**Conclusion:** PrEP continuation and objective adherence were higher in pregnancy and postpartum than in other studies of AGYW, yet many women had intermittent PrEP use. Characteristics which are associated with less optimal use may help us tailor interventions to specific age groups or specific women.

## 705 PREGNANCY AND BIRTH OUTCOMES IN PrEP-EXPOSED & UNEXPOSED PREGNANT SOUTH AFRICAN WOMEN

**Dvora Joseph Davey**[1], Dorothy C. Nyemba[2], Rufaro Mvududu[2], Nyiko Mashele[2], Linda-Gail Bekker[3], Pamina M. Gorbach[1], Thomas J. Coates[1], Landon Myer[2]
*[1]University of California Los Angeles, Los Angeles, CA, USA, [2]University of Cape Town, Cape Town, South Africa, [3]Desmond Tutu HIV Foundation, Cape Town, South Africa*

**Background:** There are few safety data on the use of oral PrEP in pregnancy presenting a barrier to PrEP implementation in some settings.

**Methods:** Based at a primary care facility in Cape Town, the PrEP in pregnancy and postpartum (PrEP-PP) study offered HIV prevention counseling and PrEP to consenting pregnant women (≥16 years) without HIV from their first antenatal care (ANC) visit through 12 months' postpartum. We compared pregnancy and birth outcomes including pregnancy loss (miscarriage, stillbirth, termination) and birth outcomes (birthweight [median], low-birth weight [<2500 grams], pre-term [<37 weeks' gestation] and neonatal death) between PrEP exposed (any PrEP use while pregnant) vs. unexposed (no PrEP use in pregnancy), abstracted from routine health records, and compared these with clinic-wide statistics from the same period. Analyses of miscarriage and stillbirth were restricted to women who entered before 20 and 28 weeks, respectively, while analysis of birth outcomes included all women with available data.

**Results:** Between August 2019 and October 2021, 850 women with pregnancy outcomes (median gestation at first ANC, 23 weeks [IQR, 14-31]; median age=26 years [IQR, 22-31]) are included of whom 95% (n=807) were PrEP exposed. Overall, 94% (n=797) had singleton live births, 94% (n=759) in the PrEP exposed group and 88% (n=38) in the PrEP unexposed group. We recorded 8% miscarriages in the PrEP exposed group vs. 7% in the unexposed group (p=0.77), and 3% stillbirths in the exposed group vs. 7% in the unexposed group (p=0.21). Among the live births in the exposed group, there were n=4 neonatal deaths (0.5%), 7% were low birthweight, 7% were preterm, and 9% were small for gestational age. There were no differences in birth outcomes between the PrEP-exposed vs. unexposed (composite adverse birth outcome=14% in both groups; p=0.99). Among the PrEP exposed, there was no association with duration of antenatal exposure and birth outcomes (p=0.84). In the clinic-wide statistics on birth outcomes in HIV-uninfected women, the frequency of stillbirths, low-birthweight deliveries and neonatal deaths was similar to levels in the PrEP exposed cohort (p>0.05) (Table 1).

**Conclusion:** While the overall frequency of adverse pregnancy and birth outcomes is high in this setting, these reassuring data suggest nor differences in pregnancy outcomes comparing women exposed to PrEP to women with no exposure to PrEP.

**Table 1:** Pregnancy and birth outcomes of women ever exposed compared to women never exposed to PrEP during pregnancy, and women without HIV in referral clinic, Cape Town, South Africa

| Total of all women with pregnancy outcomes | All women in PrEP-PP study n (%) | PrEP exposed (ever) n (%) | PrEP unexposed (never) n (%) | p-value | Clinic women without HIV (n=6435) | p-value*** |
|---|---|---|---|---|---|---|
| **Pregnancy losses** | **547 (100)##** | **519 (95)** | **31 (5)** | - | | |
| Total pregnancy losses | 47 (6) | 43 (5) | 4 (9) | 0.29 | | |
| Miscarriage GA ≤ 20 weeks # | 31 (8) | 29 (8) | 2 (7) | 0.77 | | |
| Stillbirth GA > 20 weeks## | 15 (2) | 13 (3) | 2 (6.5) | 0.21 | 115 (2) | 0.25 |
| Termination## | 1 (1) | 1 (1) | 0 (0) | 0.38 | | |
| **Live birth outcomes** | **850 (100)** | **807 (95)** | **43 (5)** | - | | |
| Total live singleton births | 797 (94) | 759 (94) | 38 (88) | - | 5923 (92) | 0.68 |
| Term delivery GA ≥37wk | 733 (86) | 699 (87) | 34 (79) | 0.16 | - | - |
| Preterm delivery GA <37wks | 64 (7) | 60 (7) | 4 (9) | 0.65 | - | - |
| Neonatal death* | 4 (0.5) | 4 (0.5) | 0 (0) | 0.99 | 63 (1) | 0.66 |
| LBW< 2500g * | 61 (7) | 60 (7) | 1 (2) | 0.17 | 502 (8) ‡ | 0.86 |
| SGA < 10th percentile* | 71 (8) | 69 (9) | 2 (5) | 0.32 | - | - |
| Birth weight (median, IQR), g^ | 3200 (2900- 3600) | 3200 (2900 -3600) | 3300 (2900 - 3700) | 0.67 | 3200 (2800 -3600) | - |
| **Composite adverse outcome** | 118 (14) | 112 (14) | 6 (14) | 0.99 | 1077 (17) | **0.07** |

IQR, Interquartile range; LBW, low birthweight; GA, gestational age; SGA, small for gestational age; PrEP, pre-exposure prophylaxis
**Bold p<0.10**
# among women who entered study <20 weeks (n=377); ## among women who entered study before 28 weeks (n=547)
* among all live births
**13 live births with missing birthweight, ^ among those with birth weights recorded (n=784); ‡ n=6194 in clinic data
***p-value for the comparison of preganancy and birth outcomes between PrEP exposed and referral clinic

## 706 EVALUATION OF AN HIV-1/HIV-2 QUALITATIVE TEST FOR HIV EARLY INFANT DIAGNOSIS

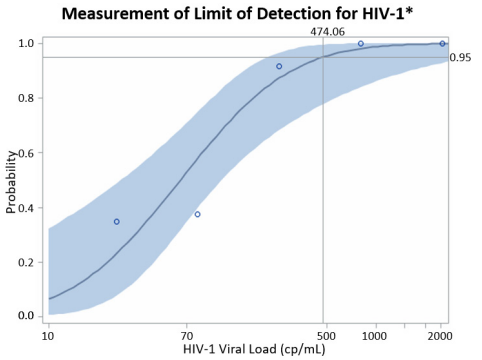
**Shuyi Li**[1], Guoqing Zhang[1], Katrina Sleeman[1], Shon Nguyen[1], Demetrius Mathis[1], Heather Alexander[1], Clement Zeh[1]
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** Early Infant Diagnosis (EID) of HIV infection is key to ending the HIV pandemic. Currently, there is no HIV-1/HIV-2 qualitative assay for EID testing on high throughput testing systems from major manufacturers. The combination of confirmatory HIV testing and differentiation of heterotypic (HIV-1/2) and homotypic (HIV-1 or HIV-2) infections into one single test will provide clinicians with critical diagnostic data for personalized management of patients with HIV. This is particularly important in West African counties. Roche has developed the cobas HIV-1/HIV-2 Qualitative Test to detect and differentiate HIV-1/HIV-2 in dried blood spots (DBS). We report here the first independent performance evaluation of the test conducted at a College of American Pathologists accredited laboratory at the US CDC as part of the WHO prequalification of in vitro diagnostics process.

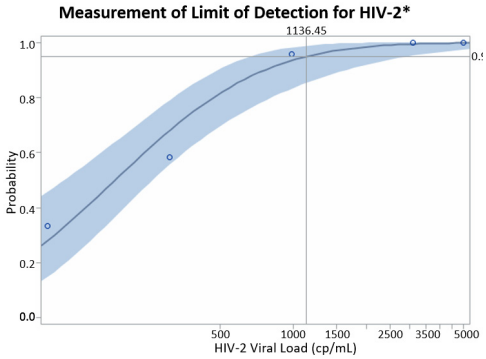
**Methods:** The evaluation used DBS created from HIV-negative whole blood spiked with cultured virus or with HIV-1 and HIV-2 RNA International WHO Standards. Prepared DBS were stored at -80°C until day of testing. Testing was performed on a cobas 6800 system (c6800) using the HIV-1/HIV-2 DBS Qual workflow and reagent kit. The limit of detection (LOD) was calculated using PROBIT analysis. The reproducibility, cross-contamination, subtype detection for HIV-1 A, B, C, D, CRF02-AG and for HIV-2, and error rate were also assessed.

**Results:** The LOD for HIV-1 was 474 copies/mL (95% confidence interval: 162 – 2,550 copies/mL), and for HIV-2 was 1,136 copies/mL (683 – 3,062 copies/mL). Testing of forty replicates of three HIV-1 or HIV-2 samples over five days, by two testers with different reagent lots, showed 100% reproducibility. The five major HIV-1 subtypes evaluated were all detected. No cross-contamination was detected and the overall error rate was 0.48% among 409 tests performed.

**Conclusion:** This evaluation verified the manufacturer's claims of analytical performance of the assay and provided valuable information for decision-making process related to approval for implementation in PEPFAR-supported countries. This is the first and only HIV-2 qualitative test commercially available on a high throughput HIV testing system. Clinical performance is currently being evaluated at PEPFAR-supported sites. The cobas HIV-1/HIV-2 Qualitative Test on the c6800 for HIV EID combines the capability of confirmatory HIV infection and HIV-1/HIV-2 differentiation, which will prove to be a useful tool in combating HIV.




* Predicted Probabilities for Frequency with 95% Confidence Limits




* Predicted Probabilities for Frequency with 95% Confidence Limits

## 707 ESTIMATING TIME OF HIV-1 INFECTION IN INFANTS USING VIRAL SEQUENCE DIVERSITY

**Magdalena Russell**[1], Carolyn S. Fish[1], Sara Drescher[1], Noah Cassidy[1], Julie Overbaugh[1], Sarah Benki-Nugent[2], Jennifer Slyker[2], Dorothy Mbori-Ngacha[3], Rose Bosire[4], Dalton C. Wamalwa[5], Elizabeth Maleche-Obimbo[5], Grace John-Stewart[2], Frederick Matsen IV[1], Dara A. Lehman[1]

*[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]University of Washington, Seattle, WA, USA, [3]United Nations Children's Fund, New York, NY, USA, [4]Kenya Medical Research Institute, Nairobi, Kenya, [5]University of Nairobi, Nairobi, Kenya*

**Background:** Infants born to mothers living with HIV are at risk for acquiring HIV in utero or during delivery and breastfeeding. Defining the time of infection typically requires regular infant testing. Adult studies have accurately estimated infection timing using rates of viral diversification, however, these models have low prediction accuracy when used for infants. Because infant HIV is associated with higher viral load than adults, we hypothesized that an infant-specific model using viral sequence diversity would more accurately predict infection time for infants than adult-specific models.

**Methods:** Using Illumina sequencing of regions within gag and pol (roughly 4 kb total) from longitudinal plasma samples collected between 1-24 months of age from 18 Kenyan infants with defined infection timing (11 infected in utero, 3 infected between 3-6 months, and 4 infected between 6-12 months), we estimated the average pairwise diversity (APD) of the viral population within each sample time-point. With these data, we designed an infant-specific Bayesian hierarchical regression model that predicts time since infection using viral APD. We validated this model using leave-one-out cross validation, and compared these estimates to infection timing estimates for each infant inferred using an existing adult-specific model (Puller et al, 2017).

**Results:** APD increased at a mean rate of 0.003 diversity/year (CI = [0.001 - 0.005], p = 0.004) across all infants and sequence regions. This rate was significantly higher for infants infected in utero than infants infected after birth (0.003 vs. 0.001 diversity/year, p = 0.006). Rates also varied significantly between infants (range = -0.003-0.026, p = 1.5e-12) and sequence regions (range = 0.002-0.004, p = 0.006). We incorporated this variation into our Bayesian hierarchical model framework. As such, our infant-specific model predicts time since infection for infants more accurately (mean absolute error = 7 months) than existing adult-specific models (mean absolute error = 2.7 years).

**Conclusion:** Here, we have shown that viral APD can be used to estimate time since infection for infants more accurately using our infant-specific model compared to adult-specific models. With our Bayesian modeling approach, we can also assess the probability of all possible infection times. As such, our model will be useful for predicting time of HIV infection for infants with unknown infection timing.

## 708 COST OF AN HIV TEST-AND-TREAT STRATEGY AT BIRTH AND ITS EFFECT ON ART INITIATION

**Kira Elsbernd**[1], Issa Sabi[2], Joaquim Lequechane[3], Siriel Boniface[2], Chishamiso Mudenyanga[4], Chris W. Buck[5], Arlete Mahumane[3], Bindiya Meggi[3], Kassia Pereira[3], Mariana Müller[6], Till Bärnighausen[7], Michael Hoelscher[6], Arne Kroidl[6], Ilesh Jani[3], Stefan Kohler[7]

*[1]Klinikum der Universität München, Munich, Germany, [2]National Institute for Medical Research–Mbeya Medical Research Center, Mbeya, Tanzania, [3]Instituto Nacional de Saúde, Maputo, Mozambique, [4]Clinton Health Access Initiative, Maputo, Mozambique, [5]University of Los Angeles, David Geffen School of Medicine, Los Angeles, CA, USA, [6]Division of Infectious Diseases and Tropical Medicine, Klinikum der Universität München, Munich, Germany, [7]Heidelberg Institute of Global Health, Heidelberg University, Heidelberg, Germany*

**Background:** HIV disease progresses rapidly in neonates with mortality peaking in the first 2-3 months of life. Late diagnosis causes delays in access to antiretroviral treatment (ART), often past the mortality peak. This study assessed the cost of HIV early infant diagnosis (HEID) at birth using point-of-care nucleic acid tests (PoC-NATs) and its effect on ART initiation.

**Methods:** We conducted a microcosting study from a provider perspective at 28 primary health facilities in Mozambique and Tanzania. Cost data were collected for set-up and operations, reflecting fixed and variable costs incurred by the health system. Resource use and outcome data were derived from the LIFE Study. Intervention sites implemented PoC-NAT at birth with follow-up testing at 4-6 weeks. Comparison sites followed the standard HEID algorithm with first PoC-NAT at 4-6 weeks. Mozambique used the Abbot mPIMA platform as true bedside testing in maternity wards for HEID and maternal HIV viral load. Tanzania used the Cepheid GeneXpert platform with on-site laboratory support across several programs.

**Results:** Of 5895 HIV-exposed infants (HEI) tested, 120 were diagnosed with HIV by three months of age. HEID and ART initiation at birth was associated with a median additional cost of $37.42/infant in Mozambique and $22.69/infant in Tanzania. Consumables contributed the largest share to PoC-NAT unit costs (73-89%). Equipment costs were 6-23% of total costs in both countries, dependent on testing volume. Fewer repeat tests in Tanzania reduced costs on average by 35% compared to Mozambique. Cost sharing of the GeneXpert platform across programs in Tanzania further reduced costs by 13% overall and up to 38% at low volume sites (<10 HEID tests/month). Infants offered birth testing initiated ART a median of 4.29 weeks (95% CI: 4.00, 4.43; p<0.001) earlier compared to the standard of care group.

**Conclusion:** For perinatally infected neonates, birth testing increases costs but results in significantly earlier ART initiation, potentially to before the period of peak mortality. On-site laboratory support may decrease PoC-NAT error rates and thus reduce repeat testing costs while maintaining same-day delivery of results afforded by PoC testing. Primary health facilities with established PoC HEID programs serving large numbers of HEI or with sufficient demand for other PoC assays run on the same platform could consider birth testing to identify and link HIV-infected neonates to care earlier and potentially reduce HIV-related infant mortality.

## 709 VALIDATION OF A PEDIATRIC SCREENING TOOL TO IDENTIFY HIV-POSITVE CHILDREN IN ZAMBIA

**Jessica Joseph**[1], Felton Mpasela[2], Isaac Banda[3], Patricia M. Bobo[2], Stephanie Dowling[1], Prudence Haimbe[2], Pamfred Hasweeka[2], Gertrude S. Kampekete[3], Fredrick Mumba[2], Charles Sakulanda[3], Hilda Shakwelele[2], Mwanei Simasiku[2], Kanchana Suggu[1], Gloria Munthali[3]

*[1]Clinton Health Access Initiative, Boston, MA, USA, [2]Clinton Health Access Initiative, Lusaka, Zambia, [3]Ministry of Health, Lusaka, Zambia*

**Background:** Despite a policy of universal HIV testing for all individuals including children presenting at public health facilities in Zambia in 2017, testing coverage remains low in high-volume wards. A targeted screening approach has been shown to improve testing efficiencies and increase case findings by testing at-risk children. While some HIV screening tools are in use

among the paediatric population in Zambia, there is no validated screening tool. This study aimed to develop and validate a screening tool to improve case finding of HIV-positive children.

**Methods:** A screening tool comprised of 14 questions was created by combining questions from existing validated and non-validated pediatric HIV screening tools. Between November 2020 and September 2021, all children (ages 18 months to 14 years) presenting at outpatient departments in 30 health facilities in two provinces of Zambia were eligible; those whose guardians provided consent were screened and tested for HIV, regardless of their responses to the screening questions. The analysis used a randomly extracted 'validation' dataset (80% of all records) and cluster-adjusted multivariable logistic regression to determine the highest performing screening questions and the optimal number and combination of questions to include in a final screening tool. The final screening questions selected were then evaluated in the 'test' dataset (remaining 20% of records). Sensitivity and specificity were calculated for both datasets.

**Results:** Out of 11018 children tested, 1116 were excluded for being age-ineligible or not responding to all 14 screening questions. Among the remaining 9902, HIV prevalence was 1.3%. Six questions were found to be significantly associated with HIV-positivity. It was determined that the optimal screening cutoff score was to answer 'yes' to one or more of the six questions; using this cutoff sensitivity was 93% and specificity was 63% (Table). In the test dataset, the same tool had a sensitivity of 85% and specificity of 65%. Adopting this screening tool would decrease the number needed to test to find one HIV-positive child from 76 to 32.

**Conclusion:** The results of this study show that in a validated screening tool, asking six questions to screen children for HIV testing is expected to find 85% of all true positive children. Implementing this screening tool should more efficiently accelerate identifications of HIV-positive children. Findings will be disseminated to Ministry of Health and cooperating partners to help inform policy.

Table: Sensitivity and specificity for validation and test datasets among 9902 children screened and tested for HIV in 30 public health facilities in Zambia

| | Validation dataset (N=7922) | | Test dataset (N=1980) | |
|---|---|---|---|---|
| | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
| Screening question | | | | |
| Biological mother HIV+ or unknown status | 74% (64%-82%) | 82% (81%-82%) | 69% (48%-86%) | 82% (80%-83%) |
| 1 or more biological parents deceased | 24% (16%-33%) | 95% (95%-96%) | 23% (9%-44%) | 95% (94%-96%) |
| Child in poor health in last 3 months | 36% (27%-46%) | 95% (94%-95%) | 27% (12%-48%) | 95% (94%-96%) |
| Child has TB symptoms | 41% (31%-51%) | 86% (86%-87%) | 27% (12%-48%) | 87% (85%-88%) |
| Child has skin problems | 26% (18%-35%) | 95% (94%-95%) | 23% (9%-44%) | 95% (94%-96%) |
| Child is short or light for age | 27% (19%-37%) | 98% (98%-99%) | 23% (9%-44%) | 98% (98%-99%) |
| **Screening tool score ≥ 1** | **93% (86%-97%)** | **63% (62%-64%)** | **85% (65%-96%)** | **65% (62%-67%)** |

## 710 COMMUNITY-BASED, PEER-LED SRH SERVICES INCREASE COVERAGE IN AYP (YATHU YATHU TRIAL)

**Mwelwa Phiri**[1], Albertus Schaap[2], Lucheka Sigande[1], Rosemary Zulu-Phiri[1], Louis Mwape[1], Melvin Simuyaba[1], Sian Floyd[3], Sarah Fidler[4], Richard Hayes[3], Musonda Simwinga[1], Bernadette Hensen[3], Helen Ayles[2]

*[1]Zambart, Lusaka, Zambia, [2]London School of Hygiene & Tropical Medicine, Lusaka, Zambia, [3]London School of Hygiene & Tropical Medicine, London, UK, [4]Imperial College London, London, UK*

**Background:** Ensuring adolescents and young people (AYP) have access to comprehensive sexual and reproductive health services (SRHS), including HIV testing and prevention, is critical if we are to reduce HIV incidence and improve wellbeing. Following HPTN 071 (PopART) in Zambia, AYP stated that they needed improved access to SRHS and that these services should be provided from locations other than the health facility. The Yathu Yathu ("For us, by us") trial was co-developed from this request. We report on a secondary outcome of this trial, coverage of 6 predefined key SRHS (HIV testing, ART initiation, PrEP initiation, condom collection, VMMC and hormonal contraception) by trial arm

**Methods:** Yathu Yathu is a cluster randomized trial conducted 2019-2021 in 2 urban communities in Lusaka, Zambia. The communities were divided into 20 zones which were randomly allocated to the Yathu Yathu intervention (YY) or standard of care (SoC) arms. In intervention zones, a YY hub, staffed by supervised peers, provided SRHS. In both arms, a census was conducted in 2019 where AYP (15-24 years) were invited to participate in the trial. Each was offered a Yathu Yathu card, which allowed them to collect "prevention points" for accessing SRHS at the health facility (SoC arm) or at the hub and health facility (YY arm). In both arms, points could be exchanged for health rewards, thus acting as an incentive to access services and as a tool to record service use. We use this YY card data to assess coverage of key SRHS

**Results:** Of the 40,864 AYP enumerated, 29,370 (71.9%) consented to participate and accepted a Yathu Yathu card (14, 872, 71.6% YY arm, 14,498, 72.2% SoC arm). In the YY arm, 9493/14878 (63.8%) accessed at least one key service compared to 775/14498 (5.4%) in the SoC arm (adj RR 12.5; 95%CI 9.9-15.8, p<0.001). Results were similar by age and sex (Table 1). The median number of visits in the YY arm was 1 (IQR 0-31) compared to 0 (IQR 0-0) in SoC. Of those accessing any service, HIV testing was the most common service in both arms (8841/9493 (93.1%) and 568/775 (73.3%), respectively) followed by collection of condoms (4701/9493 (49.5%) and 386/775 (49.8%) respectively)

**Conclusion:** The Yathu Yathu intervention increased uptake of key SRHS, especially HIV testing. While YY hubs closed for 3months during COVID-19, health facility attendance may have also decreased thus affecting the difference in coverage. Nonetheless, our findings demonstrate the potential of peer-led community hubs to increase coverage of SRHS

Table 1

| Uptake of at least 1 key SRH service | Intervention | Control | Adjusted RR | p |
|---|---|---|---|---|
| Overall | 63.8% (9493/14,872) | 5.4% (775/14498) | 12.4 (9.4-16.3)* | < 0.001 |
| 15-19yo girls | 72.1% (3596/4990) | 5.5% (252/4569) | 13.8 (10.3 18.7)** | < 0.001 |
| 15-19yo boys | 68.3% (2300/3366) | 6.7% (206/3065) | 10.7 (8.2–13.8)** | < 0.001 |
| 20-24yo women | 55.2% (2404/4357) | 3.8% (174/4574) | 16.0 (11.2–22.9)** | < 0.001 |
| 20-24yo men | 55.3% (1193/2159) | 6.2% (143/2290) | 10.1 (6.0 –16.7)** | < 0.001 |

* Adjusted for age, sex and community, ** adjusted for community

## 711 2-YEAR OUTCOME OF EARLY TREATED INFANTS IN SUB-SAHARAN AFRICA

**Alfredo Tagarro**[1], Sara Domínguez-Rodríguez[1], Louise Kuhn[2], Tacilta Nhampossa[3], Kennedy Otwombe[4], Anita Janse van Rensburg[5], Nigel Klein[6], Maria Grazia Lain[7], Almoustapha I. Maiga, Camille Brehin[9], Carlo Giaquinto[10], Paolo Rossi[11], Pablo Rojo[1]

*[1]Fundación para la Investigación Biomédica del Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY, USA, [3]Centro de Investigação em Saúde de Manhiça, Maputo, Mozambique, [4]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [5]Tygerberg Children's Hospital and Family Clinical Research Unit, Stellenbosch University, Cape Town, South Africa, [6]Infection, Immunity, and Inflammation Programme, UCL Great Ormond Street Institute of Child Health, London, UK, [7]Fundação Ariel Glaser Contra O Sida Pediátrico, Maputo, Mozambique, [8]SEREFO (HIV/TB Research and Training Center), FMOS, University of STT, Bamako, Mali, [9]General Pediatrics Department, Children Hospital, Toulouse University Hospital, Toulouse, France, [10]PENTA Onlus, Padova, Italy, [11]Bambino Gesù Children's Hospital, Rome, Italy*

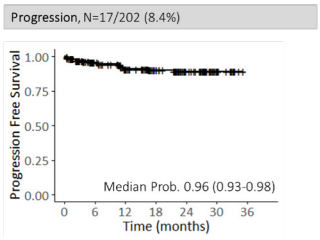
**Background:** The real-world evolution of very early treated children born with HIV in high-prevalence settings during first years of life is unclear. We assessed the probability of death, progression to AIDS, viral load (VL) suppression, immunosuppression, and continuation in care of a cohort of early treated children born with HIV.

**Methods:** EARTH-EPIICAL Cohort is underway at 2 rural and 4 urban sites in Mozambique, Mali, and South Africa (SA). Infants with HIV who started ART in the first 3 months of life, are followed at 2, 6 and 12 weeks, and then 6-monthly for 4 years. Hereby, we provide the probability of death, progression, suppression and continuation in care during the first 2 years of life with multivariable cox regression models were used. Backward stepwise elimination was applied to reach the final multivariable model.

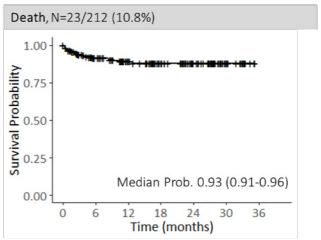
**Results:** 212 participants were enrolled and followed during a median time of 17 [6.8;27.5] months; 84 reached 2 years of follow-up. ART started at 34 [26;74] days of life, mostly 3TC+ABC+LPV/r (65%). Adherence was suboptimal (<90%) in 56% of visits. 23 patients (10.8%) died, at a median of 2.5 [0.6;6.8] months of age. At 2 years, probability (P) of death was 12% (CI95%,7 to 17), (P) of progression was 11% (CI95%,6 to 16%), (P) of continuation in care, 80% (CI95%,74 to 86%), (P) of VL suppression was 46% (CI95%, 0.34-0.49), and (P) of severe IS, 54% (CI95%, 44 to 62). Death occurred predominantly in the first 6 months (74%); mostly due to pneumonia (43%), malnutrition (13%) or diarrhea (8.7%). (P) of death was associated with baseline VL 2.19 (1.4-3.3), and suboptimal adherence 2.88 (1.18-7.2). (P) of progression was associated with baseline VL 1.71 (CI95%,1.14-2.58), and weight for age 0.53 (CI95%,0.39-0.71). (P) of lost to follow up also was associated with baseline VL (HR, 1.60 (CI95%,1.06-2.40) and weight for age (HR, 1.67 (CI95%,1.11-2.50). (P) of suppression associated with baseline VL (HR, 0.60 (CI95%,0.51-0.71) and

CD4% (HR, 1.04, (CI95%,1.01-1.06), p=0.01. (P) of severe IS was associated with baseline VL, (HR, 1.4 (CI95% 1.15-1.69), baseline CD4% (HR, 0.91 (0.88-0.93), baseline weight for age (HR, 0.86 (CI95%, 0.76-0.99), and Mozambique (HR 1.88 (CI95%, 1.16-3.1).

**Conclusion:** Despite early treatment and a close follow-up, death, progression, and severe IS remain high in children born with HIV in Africa, especially in the 6 first months. Additional strategies are required to improve the care of this population.




| Time (months) | Number at risk | Prob.PFS |
|---|---|---|
| 6 | 152 | 0.96 (0.93-0.99) |
| 12 | 126 | 0.91 (0.87-0.96) |
| 18 | 93 | 0.90 (0.86-.0.95) |
| 24 | 62 | 0.89 (0.84-.0.94) |
| 30 | 23 | 0.89 (0.84-.0.94) |




| Time (months) | Number at risk | Prob.Survival |
|---|---|---|
| 6 | 161 | 0.92 (0.88-0.96) |
| 12 | 135 | 0.89 (0.85-0.94) |
| 18 | 102 | 0.88 (0.83-.0.93) |
| 24 | 70 | 0.88 (0.83-.0.93) |
| 30 | 27 | 0.88 (0.83-.0.93) |

## 712 HIV-1 RESERVOIR CELL EVOLUTION IN EARLY-TREATED CHILDREN IN BOTSWANA

New Investigator Scholar

**Ciputra A. Hartana**[1], Pilar Garcia-Broncano[1], Yelizaveta Rassadkina[1], Xiaodong Lian[1], Chenyang Jiang[1], Kevin B. Einkauf[1], Sikhulile Moyo[2], Terence Mohammed[2], Comfort Maphorisa[2], Joseph Makhema[2], Ce Gao[1], Xu Yu[1], Daniel Kuritzkes[3], Roger L. Shapiro[4], Mathias Lichterfeld[1]

*[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [3]Brigham and Women's Hospital, Boston, MA, USA, [4]Harvard Medical School, Boston, MA, USA*

**Background:** Despite remarkable advances in prevention of vertical HIV-1 transmission and antiretroviral drug development, pediatric HIV-1 infection remains a frequent and difficult-to-treat disease. Early initiation of antiretroviral therapy (ART) in neonates infected with HIV-1 may limit the frequency and stability of HIV-1 reservoir cells, possibly improving response to interventions aimed at viral eradication and cure. Here, we report parallel assessments of HIV-1 reservoir cells and antiviral immune responses in children infected with HIV-1 who started early ART.

**Methods:** 37 children from the Early Infant Treatment cohort in Botswana, who started ART at a median of 2 days from birth, were included in this study. HIV-1 near full-length genome sequencing of individual proviral species were used to characterize the proviral reservoir landscape. Integration sites associated with each proviral sequence were obtained using Matched Integration site and Proviral Sequencing (MIP-Seq). Immune responses were measured using flow cytometry.

**Results:** At birth, the frequency of intact proviruses was inversely associated with IL-8-secreting CD4 T cells, which represent a dominant cell subset in neonates and displayed higher levels of cell-intrinsic resistance to HIV-1 infection. After 84-96 continuous weeks of treatment, proviral DNA levels had decreased by 5-10 fold; this decrease was significantly more pronounced for intact compared with defective HIV-1 proviruses ($p = 0.0209$). The decline of intact proviruses was inversely associated with an expansion of CD57+ NK cells, characterized by enhanced cytotoxic activities. Conversely, proportions of NK cells expressing the inhibitory receptor NKG2A decreased over time and correlated positively with intact provirus frequency. In two study participants, intact proviruses at week 84 were frequently integrated in heterochromatin regions that represent atypical sites for proviral integration during primary infection; these same integration sites have been observed in persons with natural immune control of HIV-1.

**Conclusion:** Together, these results suggest that HIV-1 reservoir cell seeding and evolution in early-treated children is markedly influenced by innate immune responses.

## 713 DIFFERENTIAL CLEARANCE OF INTACT AND DEFECTIVE HIV DNA IN THE PEDIATRIC RESERVOIR

**Makayla Poindexter**[1], Carolyn S. Fish[2], Noah Cassidy[2], Elizabeth R. Duke[2], Dalton C. Wamalwa[3], Agnes Langat[3], Daisy J. Chebet[3], Hellen Moraa[3], Jennifer Slyker[4], Sarah Benki-Nugent[4], Grace John-Stewart[4], Joshua Schiffer[2], Dara A. Lehman[2], Daniel B. Reeves[2]

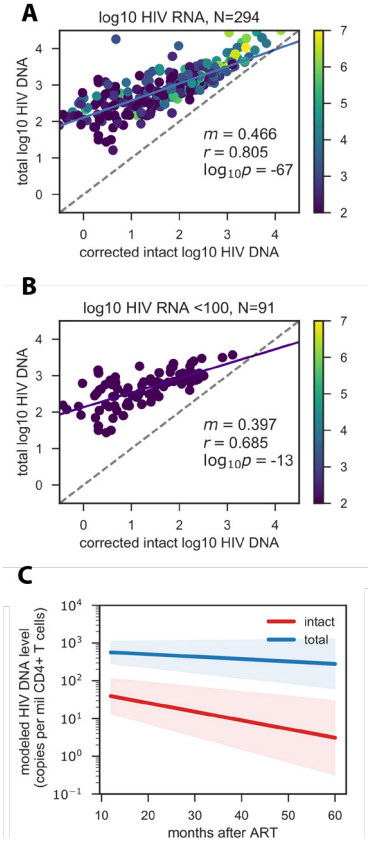
*[1]North Carolina State University, Raleigh, NC, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]University of Nairobi, Nairobi, Kenya, [4]University of Washington, Seattle, WA, USA*

**Background:** To date, studies of HIV reservoir dynamics in pediatric infection have been small and predominately limited to total HIV DNA measurements. It remains unclear if proviral sequence fidelity (intact vs defective) affects reservoir clearance in children – intact proviral DNA assays (IPDA) allow better approximations of the rebound-competent HIV reservoir.

**Methods:** We analyzed data from children living with HIV (CWH) in Nairobi, Kenya who initiated early ART, including longitudinal viral RNA levels as well as intact and total HIV DNA quantified using a cross-subtype IPDA. To accurately model HIV reservoirs, we restricted to time points with undetectable viral replication: HIV RNA <150 copies/mL.HIV DNA half-lives were estimated by log-linear mixed effects modeling.

**Results:** Across individuals, $\log_{10}$ total and $\log_{10}$ intact HIV DNA were strongly correlated (Pearson r=0.8; p = 10-67, Fig 1A). This relationship persists in a subset of data with HIV RNA <150 copies/mL (Pearson r=0.68; p = 10-13, Fig 1B). In both cases, the slope of the correlation (m~0.4) implies the ratio of intact to total HIV DNA decreased as total HIV DNA decreased. This observation may be related to more rapid clearance of intact HIV DNA relative to defective HIV DNA during ART, motivating the longitudinal modeling. Of 141 CWH who started ART in the first year of life, 38 satisfied longitudinal modeling inclusion criteria. Using suppressed time points in the first 60 months of ART, we estimated an intact HIV DNA half-life of 13 months (95% CI 9 to 24) and a total HIV DNA half-life of 47 months (95% CI 22 to ∞, i.e., was inclusive of increasing levels) (Fig 1C).

**Conclusion:** Together, these observations suggest that children exhibit differential reservoir clearance based on sequence fidelity, i.e., intact (replication-competent) HIV clears faster than total (includes defective) HIV DNA. The rates are generally faster than comparable estimates from adults, suggesting a direct comparison of estimates made with identical methods (including multiple-phase modeling) is warranted.



## 714 LOWER RESERVOIR CONTRIBUTION OF NAÏVE VS. MEMORY T CELLS IN PERINATAL HIV INFECTION

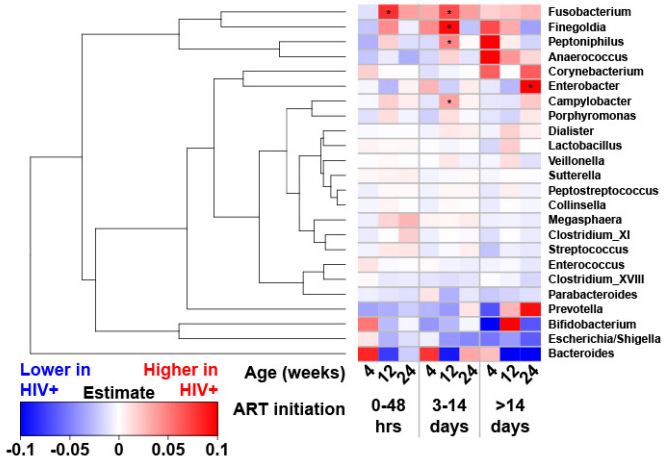
**Adit Dhummakupt**[1], Yuyang Huang[1], Joseph Szewczyk[1], Priya R. Khetan[1], Ya Chen[1], Hao Zhang[2], Bareng A. Nonyane[2], Thuy Anderson[1], Mareike Haaren[1], Vicki Tepper[3], Allison Agwu[1], Deborah Persaud[1]
*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]University of Maryland, Baltimore, MD, USA*

**Background:** Recent studies in adults and SIV-infected infant rhesus macaques underscore naïve CD4+ T cells as an important HIV-1 reservoir. Naïve T cells are dominant during infancy when HIV-1 reservoirs are formed. We posit that naïve compared with memory CD4+ T cell reservoirs may be larger in perinatal infection.
**Methods:** Proviral reservoirs in memory and naïve T cells were quantified in 10 youths (median age 15.4 yrs, IQR 13.5-17.8) with perinatal HIV-1 and known inducibility in the latent reservoir. Total CD4+ T cells were purified from peripheral blood mononuclear cells and stained with CD3, CD4, CCR7, CD45RA, and CD95. Naïve (CD3+, CD4+, CCR7+, CD45RA+, and CD95-) cells were sorted and the remainder collected as the memory fraction. Genomic DNA was isolated and HIV-1 infection frequencies quantified with the Intact Proviral DNA Assay (IPDA). Near full-length proviral sequences were amplified in limiting dilution followed by nested HIV-1 env amplification and Sanger sequencing. Co-receptor tropism usage was analyzed with WebPSSM and statistical analyses were performed using non-parametric paired sample tests, significance determined at $p<0.05$.
**Results:** Naïve CD4+ T cell median prevalence was 63% (IQR 45-71%). HIV-1 DNA was detected in all 10 participants' memory cells and in 7 participants' naïve cells [median 840.9 copies/$10_6$ cells, IQR (185.7-1356.0) vs 17.3, (6.3-85.0); $p=0.002$]. Intact proviruses were detected in 9 participants' memory cells and 4 participants' naïve cells [median 37.6 copies/$10_6$ cells, (10.8-86.6) vs 5.9 (3.6-8.6); $p=0.01$]. After adjusting for individual differences in proportions of naïve and memory cells, the median proviral load in memory cells remained higher (median 267.3 copies/$10_6$ cells, IQR 78.0-480.8) compared with 13.4 copies/$10_6$ cells in naïve cells (IQR 3.0-33.3, $p=0.002$). However, the proportion of intact proviruses were higher in naïve (median 3.0 copies/$10_6$ cells, IQR 1.7-5.0) compared with memory cells (median 10.8, IQR 4.4-28.6; $p=0.006$), 19.9% vs 5.9% respectively. HIV-1 env sequencing from sorted cells revealed R5 tropism in naïve and memory cells with lower diversity in naïve compared with memory cells.
**Conclusion:** As in adults, an HIV-1 reservoir exists in naïve CD4+ T cells in perinatal infection, with higher fractions of intact proviruses and less diversity, but lower overall contribution to reservoir size. This finding provides insights into HIV-1 reservoir generation and maintenance in longstanding perinatal infection.

## 715 EARLY ANTIRETROVIRAL THERAPY IN NEONATES AND MATURATION OF THE GUT MICROBIOME

**Louise Kuhn**[1], Fan Li[2], Renate Strehlau[3], Nicole Tobin[2], Faeezah Patel[3], Stephanie Shiau[4], Shuang Wang[1], Elaine J. Abrams[5], Caroline T. Tiemessen[6], Grace M. Aldrovandi[2]
*[1]Columbia University Medical Center, New York, NY, USA, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]University of the Witwatersrand, Johannesburg, South Africa, [4]Rutgers University, Piscataway, NJ, USA, [5]ICAP at Columbia University, New York, NY, USA, [6]National Institute for Communicable Diseases, Johannesburg, South Africa*

**Background:** In the pre antiretroviral therapy (ART) era, breastfeeding has been associated with improved survival outcomes among infants with perinatally-acquired HIV infection. Breastfeeding is known to support optimal establishment of a healthy gut microbiome. Here we investigated whether breastfeeding and early ART mitigate harmful influences of intrauterine HIV infection on the developing infant microbiome.
**Methods:** At one site in Johannesburg, South Africa, 79 infants (39 female) with intrauterine HIV infection diagnosed <48 hours of birth and 71 uninfected infants (37 female) born to women living with HIV were recruited. Infants with HIV were started on ART as soon as possible, half <48 hours of birth and the other half a median of 6 days of age. Uninfected infants received standard of care prophylaxis. Sequential rectal swab samples were collected at 4, 12 and 24 weeks of age. Microbiome profiling was performed by sequencing of the V4 region of the 16S rRNA gene, followed by denoising and exact sequence inference using DADA2. Statistical comparisons were performed using linear mixed effects models with independent probability of treatment weighting to control for potential confounding variables.
**Results:** HIV infection was associated with significant shifts in taxa including increases in Bacteroides, Fusobacterium and Finegoldia abundances after adjusting for sex, birthweight, mode of delivery, maternal viral load and maternal ART. If ART was started later than 14 days of age, this pattern was exacerbated with decrease in Bifidobacterium abundance at 4 weeks, and increase in Fusobacterium and Enterobacter abundances at later time points. Breastfeeding was associated with increases in Bifidobacterium at 4 weeks and decrease in Bacteroides abundances at later time points. When combined with early ART, breastfeeding was associated with minimizing loss of Bifidobacterium and buffering against Bacteroides expansion, although increases in Fusobacterium abundances persisted.
**Conclusion:** There are detectable benefits associated with breastfeeding in conjunction with early ART in maintaining a more Bifidobacteria-rich microbiota profile in infants with HIV. However, persisting shifts in the microbiota profile despite early ART, even among breast-fed infants, support the need for complementary interventions to strengthen early ART and improve outcomes.



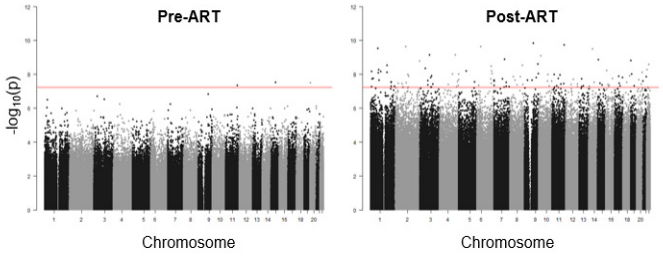

## 716 DNA METHYLATION SIGNATURES ASSOCIATED WITH HIV SUPPRESSION AFTER TREATMENT IN INFANTS

**Stephanie Shiau**[1], Ziyi Wang[1], Renate Strehlau[2], Ashraf Coovadia[2], Carmen Marsit[3], Shuang Wang[4], Michael T. Yin[4], Stephen M. Arpadi[4], Elaine J. Abrams[4], Louise Kuhn[4]
*[1]Rutgers University, Piscataway, NJ, USA, [2]University of the Witwatersrand, Johannesburg, South Africa, [3]Emory University, Atlanta, GA, USA, [4]Columbia University Medical Center, New York, NY, USA*

**Background:** No studies have examined epigenetic changes in the context of early antiretroviral therapy (ART) in infants with HIV. We tested if blood DNA methylation (DNAm) profiles pre- and post-ART are different between infants who do and do not achieve viral suppression by 1 year on ART.
**Methods:** We selected samples from 75 early-treated infants with HIV who initiated LPV/r-based ART <6 months of age as part of a clinical trial in Johannesburg, South Africa, including 48 who achieved viral suppression, defined as attaining plasma HIV-1 RNA <400 copies/ml for ≥3 months within the first 12 months of ART (suppressed), and 27 who did not (unsuppressed). DNAm on peripheral blood mononuclear cells collected pre-ART and ~6 months post-ART was assayed using the Infinium MethylationEPIC array (Illumina, San Diego, CA). Pre-processing was performed with the ewastools package in R. We tested for differentially methylated CpG sites (Bonferroni-corrected) between suppressed and unsuppressed groups pre- and post-ART using the limma package, adjusted for sex. We also tested for changes in methylation on CpG sites between the two timepoints, within group.
**Results:** Mean ages pre-ART (4.4 vs. 4.6 months, NS) and post-ART (10.5 vs. 9.3 months, NS) were similar between the suppressed and unsuppressed group, as was the proportion of females (54.2 vs. 44.4%, NS). 75% had a pre-ART viral load >750,000 copies/ml and pre-ART CD4 % was higher in the suppressed vs. unsuppressed group (24.6 vs. 18.9%, $p=0.02$). Pre-ART, there were 3 differentially-methylated CpG sites between the two groups corresponding to 3 unique genes (SMAD6, FERMT1, SIK3) (Figure). SMAD6 is upregulated

by interaction between HIV envelope protein gp120 and α4β7 interaction. Post-ART, there were 118 differentially-methylated CpG sites between groups corresponding to 66 genes, including SMAD6 and SIK3 (Figure). The suppressed group experienced a large number of changes in DNAm from pre- to post-ART (988 sites significantly different between timepoints). Changes from pre- to post-ART were not detected in the unsuppressed group (0 sites different).
**Conclusion:** Epigenetic signatures by 6 months after initiating LPV/r-based ART distinguished early-treated infants who attained suppression from those who did not. Before ART initiation, few epigenetic differences were present between infants who went on to suppress or not. Further interrogation may provide insight into specific epigenetic signatures of ART regimens or viral control in early-treated infants.

**Figure: Manhattan plot of DNA methylation CpG sites associated with HIV suppression in early-treated infants at pre- and post- ART; the x-axis represents the genomic location of the individual probes and the y-axis represents the -log 10 (p-values)**

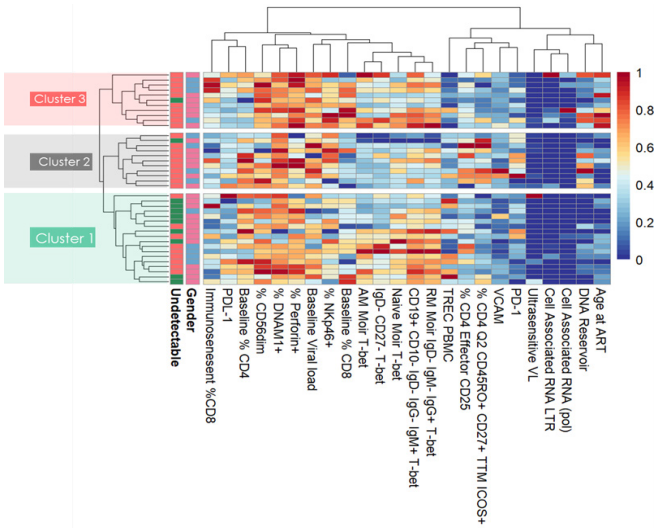



## 717 THE SUBPHENOTYPES OF EARLY-TREATED CHILDREN LIVING WITH HIV-1

New Investigator Scholar

**Sara Domínguez-Rodríguez**[1], Alfredo Tagarro[1], Caroline Foster[2], Paolo Palma[3], Nicola Cotugno[3], Anita De Rossi[4], Annalisa Dalzini[5], Savita G. Pahwa[6], Eleni Nastouli[7], Kathleen Gärtner[7], Anne Genevieve Marcelin[8], Paolo Rossi[3], Carlo Giaquinto[4], Pablo Rojo[1]
*[1]Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Imperial College Healthcare NHS Trust, London, UK, [3]Bambino Gesu Children's Hospital, Rome, Italy, [4]University of Padova, Padova, Italy, [5]University of Padua, Padova, Italy, [6]University of Miami, Miami, FL, USA, [7]University College London, London, UK, [8]Hôpitaux Universitaires Pitié Salpêtrière, Paris, France*

**Background:** Subphenotypes have been identified in several heterogeneous diseases. Having a specific subphenotype often has therapeutic implications or impacts disease progression. In this study, we aimed to assess if children with HIV may show subphenotypes according to clinical, virological and immunological features.
**Methods:** We collected data from 40 HIV+ children included in a cross-sectional multicentric study (CARMA Study, EPIICAL Consortium). All children commenced ART <2 years, suppressed (viral load (VL) <50 copies/ml) within 12 months and remained suppressed for >5 years. Immunological and virological assays were performed at a median of 12 years after ART initiation. We collected clinical and sociodemographic data, baseline VL, CD4 and CD8 data, age at ART, HIV DNA reservoir size, cell-associated RNA (CA-RNA), ultrasensitive VL, CD4 subsets (T effector CD25+, activated memory cells, Treg cells), humoral-specific HIV response (T-bet B cells), innate response (CD56dim NK cells, NKp46+, perforin), exhaustion markers (PD-1, PD-L1, DNAM), CD8 senesence, and biomarkers for T-lymphocyte thymic output (TREC) and endothelial activation (VCAM). To build the subphenotypes, the most informative variables were selected using an unsupervised penalty selection. Hierarchical clustering was performed using Pearson correlation as distance metric and Ward.D2 as clustering method. Internal validation was applied to select the best number of clusters.
**Results:** Three subphenotypes were revealed (Cluster 1 n=18, 45%; Cluster 2 n=11, 27.5%; Cluster 3 n=11, 27.5%). Cluster 1 (best controllers) consisted of early ART-treated patients with high baseline %CD4, low reservoir size, low WB score, high TREC values, and low VCAM values. In contrast, Cluster 3 (worst controller) consisted of later ART-treated patients with low baseline %CD4, high reservoir size, low TREC values, high innate response, immunosenescence markers and VCAM. Cluster 2 (low-level viremia, altered immune response) consisted of early-treated patients with low-level (10 to 50 c/mL) VL, high reservoir size but low CA-RNA, higher Treg CD4 than in the other clusters, low TREC, weak innate response and lower levels of T-bet expression.
**Conclusion: Three** subphenotypes with decreasing levels of viral control and increasing levels of immune well-being were discovered. Response to different therapies may be different across the different clusters.




## 718 IS ROUTINE PCP PROPHYLAXIS NEEDED IN VERY EARLY-TREATED INFANTS WITH HIV?

**Bryan S. Nelson**[1], Camlin Tierney[1], Deborah Persaud[2], Jennifer Jao[3], Mark F. Cotton[4], Yvonne Bryson[5], Kira Bacon[6], Diane Costello[5], Charlotte Perlowski[7], Maria Leticia Santos Cruz[8], Josphat Kosgei[9], Sai Majji[10], Dwight E. Yin[11], Ellen G. Chadwick[3]
*[1]Harvard TH Chan School of Public Health, Boston, MA, USA, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA, [4]Stellenbosch University, Tygerberg, South Africa, [5]University of California Los Angeles, Los Angeles, CA, USA, [6]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [7]FHI 360, Durham, NC, USA, [8]Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil, [9]Walter Reed Project–Kericho, Kericho, Kenya, [10]National Institute of Child Health and Human Development, Bethesda, MD, USA, [11]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

**Background:** Global guidelines recommend cotrimoxazole (CTX) prophylaxis for the 1st year of life to prevent Pneumocystis jirovecii pneumonia (PCP) in infants with HIV. However, infants are increasingly diagnosed and given antiretroviral therapy (ART) shortly after birth, preserving CD4 counts and possibly reducing risk of PCP. We summarize CD4 counts and percentages over the 1st year of life for very early-treated infants with in utero HIV who achieved and maintained virologic suppression.
**Methods:** Fifty-four infants with in utero HIV infection were followed in the IMPAACT P1115 study of very early ART, 34 born to high-risk mothers and treated presumptively with nevirapine (NVP)-based ART within 48 hours of life (Cohort 1) and 20 enrolled after HIV diagnosis by 10 days of age, having received a 3-drug NVP-based regimen from 48 hours of life until study entry (Cohort 2). Lopinavir/ritonavir was added when age-appropriate; NVP was discontinued 12 weeks after confirmed virologic suppression. Infants who did not suppress viral load <200 c/mL by 24 weeks or did not maintain viral load <200 c/mL after 24 weeks were discontinued from follow-up. CTX was given per local guidelines. CD4 was measured at entry and at weeks 2, 12, 24, 36, and 48. We report proportions with exact binomial confidence intervals (CI) as appropriate.
**Results:** Infants were enrolled primarily in Africa (97% Cohort 1, 70% Cohort 2); 68% in Cohort 1 and 50% in Cohort 2 were female. The median earliest CD4 count (CD4%) was 2,417 (52%). Thirty-nine (72% of 54) infants initiated CTX and continued for a median (Q1, Q3) of 31 (15, 43) weeks. No PCP was reported over 1,561 person-weeks of follow-up in Cohort 1 and 814 person-weeks in Cohort 2. At weeks 24 and 48, 75% (95%CI 57%-89%) and 78% (95%CI 56%-93%) of Cohort 1 infants and 100% (95%CI 81%-100%) and 83% (95%CI 52%-98%) of Cohort 2 infants had both CD4 cell count ≥1500 cells/mm$_3$ and CD4 percentage ≥25% (Figure).
**Conclusion:** The majority of infants treated shortly after birth with suppressive ART maintain high CD4 cell counts and percentages through their 1st year of life. Routine PCP prophylaxis guidelines for infants with consistently high CD4 cell counts/percentages in settings where malaria or severe bacterial infections are not highly prevalent may warrant re-evaluation.

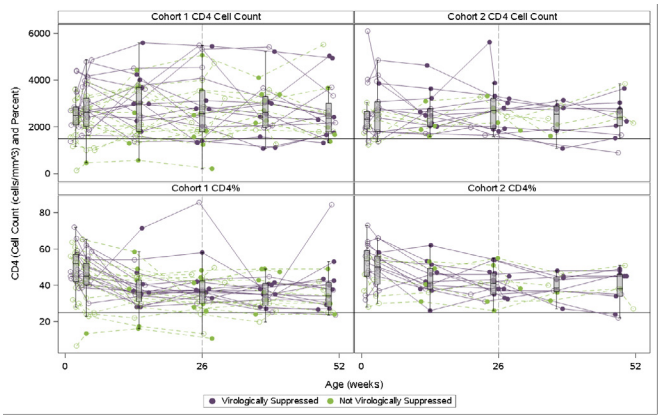



**Figure. Profile Plots of CD4 Cell Counts and CD4 Percentages**
*The dashed vertical line corresponds to the week 24 visit, at which point only infants with HIV RNA viral load <200 c/mL are followed.*
*Horizontal lines at 1500 cells/mm and 25% respectively.*
*Filled circles indicate participant was on CTX at the time of CD4 measurement.*
*Not Virologically Suppressed = RNA viral load ≥200 c/mL at 24 weeks or confirmed detectable viral load thereafter.*

## 719 SEVERE IMMUNE SUPPRESSION AND RETENTION AMONG INFANTS IN SOUTH AFRICA

**Gabriela E. Patten**[1], Nosisa Sipambo[2], Karl-Günter Technau[3], Jonathan Euvrard[1], Nathan Ford[4], Mary-Ann Davies[1]
*[1]University of Cape Town, Cape Town, South Africa, [2]Harriet Shezi Children's Clinic, Johannesburg, South Africa, [3]Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa, [4]World Health Organization, Geneva, Switzerland*

**Background:** Following rapid improvements in HIV programs, children are now starting antiretroviral therapy (ART) younger and healthier. Among infants, sustained retention and adherence to ART is especially challenging, and it is possible that severe immune suppression (SIS) will be increasingly seen among those on ART. We aimed to describe SIS and retention among infants on ART.
**Methods:** Using data from 3 International epidemiology Databases to Evaluate AIDS (IeDEA) Southern Africa cohorts, we describe SIS at ART start and on ART between 2007-2020. We included infants <1 year with a CD4 at ART start and ≥1 subsequent measure, and ≥9 months between ART start and database closure (October 2018 – March 2021). We defined lapse in care as >9 months with no visit. A multistate model was used to estimate transition probabilities between 5 states based on CD4 count/% after ART start: SIS on ART, as per WHO definition; Stable, not SIS; Early Lapse, lapse occurring <9 months from ART start; Late Lapse, lapse occurring ≥9 months on ART; and Death.
**Results:** Among 1206 infants, 53% were female. New ART initiations declined (2007-2009: 473, 2010-2012: 367, 2013-2020: 366). Overall 75% started ART with SIS. Prevalence declined, but remained very high (2007-2009: 82%, 2010-2012: 73%, 2013-2020: 66%). The proportion who ever experienced SIS on ART initially declined but plateaued after 2010 (2007-2009: 48%, 2010-2012: 40%, 2013-2020: 40%). Experiencing viremia (VL>1000 copies/ml) on ART increased (2007-2009: 58%, 2013-2020: 61%). Those starting ART in the most recent years were more likely to transition from Early lapse to SIS on ART. Later year was associated with increasing transition from Stable to Late Lapse. Those with SIS at ART start were more likely to transition from Stable to SIS on ART, and less likely to transition to Stable from SIS on ART. Those with viremia were more likely to transition from Stable to SIS on ART, and more likely to transition from either of the on ART states to Late Lapse and Death. (Table)
**Conclusion:** SIS among infants accessing ART has significantly reduced, but remains extremely high. Infants starting ART most recently are particularly vulnerable, being more likely to re-engage in care with SIS following an early lapse. Despite declining numbers, long-term retention is increasingly a challenge among those who become clinically stable. Viraemia strongly predicted death even from a clinically stable state, highlighting the difficulties of managing effective ART among infants.

**Table2: Adjusted Hazard Ratios from multivariate multistate model, aHR (95% CI) among infants initiating ART in South Africa**

| Transition | Female sex (vs male) | Year of ART start (vs 2007-2009) | | SIS at ART start | Viral load (vs VL<1000 copies/ml) | |
|---|---|---|---|---|---|---|
| | | 2010-2012 | 2013-2020 | | VL≥1000 | VL missing |
| Early Lapse - SIS | 1.14 (0.55-2.37) | 1.16 (0.43-3.11) | **2.68 (1.03-7.02)** | 1.32 (0.55-3.18) | 1 (1-1) | 1 (1-1) |
| Early Lapse - Stable | 0.65 (0.29-1.45) | 0.43 (0.17-1.07) | 0.53 (0.19-1.51) | **0.26 (0.11-0.6)** | 1 (1-1) | 1 (1-1) |
| Early Lapse - Death | 0.02 (0.0-310387.61) | 0.01 (0-723472.6.87) | 0.01 (0-134042593.08) | 4.83 (0-1156496271.63) | 1 (1-1) | 1 (1-1) |
| SIS - Stable | 1.09 (0.9-1.31) | 0.86 (0.69-1.08) | 1.17 (0.92-1.49) | **0.62 (0.47-0.82)** | 1.16 (0.94-1.42) | 1.02 (0.69-1.5) |
| SIS - Late lapse | 0.99 (0.64-1.52) | 1.26 (0.75-2.1) | 1.63 (0.94-2.83) | 0.72 (0.37-1.38) | **1.84 (1.16-2.9)** | 2.1 (0.94-4.65) |
| SIS - Death | 1.22 (0.4-3.69) | 0.74 (0.18-2.97) | 1.06 (0.29-3.91) | 0.97 (0.12-7.72) | **11.03 (2.39-50.81)** | 0.03 (0-3023172536.05) |
| Stable - SIS | 0.88 (0.63-1.22) | 0.8 (0.54-1.19) | 1.03 (0.65-1.61) | **1.76 (1.1-2.83)** | **2.44 (1.66-3.59)** | 1.89 (0.97-3.68) |
| Stable - Late lapse | 0.98 (0.85-1.13) | **1.49 (1.27-1.76)** | **2.05 (1.71-2.44)** | 1.11 (0.94-1.31) | **1.3 (1.08-1.57)** | **1.43 (1.07-1.91)** |
| Stable - Death | 1.84 (0.45-7.41) | 1.86 (0.37-9.38) | 3.08 (0.6-15.87) | 1.38 (0.28-6.8) | **5.74 (1.42-23.14)** | 3.62 (0.38-34.06) |

Bold indicates statistical significance
*SIS: Severe immune suppression: Age <11months CD4%<25% or CD4 count <1500 cells/μL; 12-35 months CD4%<20%, CD4 <750 cells/μL; 36-59 months CD4% <15%, CD4 <350 cells/μL; >60 months , CD4<200 cells/μL
**Not shown: transitions from late lapse

## 720 HIGH PREVALENCE OF HIV DRUG RESISTANCE AMONG NEWLY DIAGNOSED CHILDREN 0-18 MONTHS

**Immaculate Mutisya**[1], Leonard Kingwara[2], Jacques Muthusi[3], Evelyn Ngugi[3], Lazarus Momanyi[2], Frankline Mboya[4], Sasi Jonnalagadda[1], Winfred Nyanya[2], Grace Akinyi[5], Kimberly D. McCarthy[6], Abraham Katana[6], Lucy Nganga[6], Marc Bulterys[6]
*[1]Centers for Disease Control and Prevention, Nairobi, Kenya, [2]National AIDS and STD Control Programme, Nairobi, Kenya, [3]US Centers for Disease Control and Prevention Nairobi, Nairobi, Kenya, [4]Centers for Disease Control and Prevention, Atlanta, GA, USA, [5]Kenya Medical Research Institute-UCSF Infectious Disease Research Training Program, Kisumu, Kenya, [6]Centers for Disease Control and Prevention Nairobi, Nairobi, Kenya*

**Background:** Exposure to maternal antiretroviral treatment (ART) and infant postnatal antiretroviral (ARV) prophylaxis risks emergence of pre-treatment drug resistance (DR) in children who get breakthrough HIV infection through mother to child transmission. We estimated the national prevalence of pre-treatment HIV DR among newly diagnosed HIV-infected infants 0 to 18 months in Kenya.
**Methods:** A nationally representative cross-sectional survey of prevalence of pre-treatment HIV DR was conducted from June to December 2018 among newly diagnosed HIV infected children 0 to 18 months by polymerase chain reaction. Dried blood spot (DBS) samples underwent nucleic acid extraction using EasyMag system and Sanger sequencing to assess for the presence of DR to nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase (NNRTI), and protease inhibitors (PI). Prevalence of single DR mutations (SDRMs) was expressed as a weighted percentage and multivariate age-adjusted logistic regression was done to obtain odds ratios (OR) and 95% confidence intervals (CI) for risk factors for SDRM. All analyses were weighted per survey design.
**Results:** Of the 481 PCR positive DBS samples from children 0-18 mo, 479 met inclusion criteria. The median age at diagnosis was 20.5 weeks (interquartile range (IQR): 7.5 - 41.9). Exposure to maternal ART, infant ARV postnatal prophylaxis or both was observed in 80.2%, 60.4 %, and 53.0%, respectively. Samples from 330 (69.3%) of the children were amplified and sequenced, of which 147 (43.6%) showed SDRMs: 144 (42.1%), 27(7.8%), and 6 (1.8%) to NNRTIs, NRTIs, and PIs, respectively (Table 1). After adjusting for infant age, SDRMs were associated with the use of maternal ART and infant prophylaxis compared to those who were unexposed (adjusted OR: 2.9; 95 % CI: 1.3-6.6). Odds of SDRM in infants exposed to PI-based maternal ART was 10.5 (95% CI: 1.9-57.0), compared to 4.6 (95% CI: 1.3-16.2), and 2.0 (95% CI: 1.0-3.9) in nevirapine and efavirenz-based maternal ART regimens, respectively.
**Conclusion:** Nearly half of newly diagnosed HIV infected children in Kenya had one or more HIV DR mutations. Children born to women on PI based regimens had a higher risk of SDRMs. These results, support the 2021 WHO ART guidelines for children and women of reproductive age and call for optimal post-natal infant prophylaxis and routine DR surveillance among pre-treated HIV infected children.

Table 1: Frequency of major drug resistant mutations among pre-treatment HIV-infected Kenyan infants by class among all amplified samples (n=330)

| NRTI Major (N = 60) | n (%) | NNRTI Mutations (N = 181) | n (%) | PI Mutations (N = 6) | n (%) |
|---|---|---|---|---|---|
| M184V/I | 12 (24) | K103N/S | 100 (55) | I85V | 2 (33) |
| D67G/N | 6 (12) | P225H | 8 (4) | M46L | 1 (17) |
| T69D | 1 (2) | Y181C/V | 30 (17) | L90M | 3 (50) |
| K70R/E | 6 (12) | V106M/A | 4 (2) | | |
| T215I/C/F | 6 (12) | G190A/E | 24 (13) | | |
| K219E/R/Q/N | 10 (20) | K101E/P | 7 (4) | | |
| L74I/V | 4 (8) | V179F | 1 (1) | | |
| K65R | 3 (6) | Y188L/HL | 6 (3) | | |
| V75A | 1 (2) | L100I | 1 (1) | | |
| M41L | 1 (2) | | | | |

*Percentages are weighted

## 721 LIVING: 48-WEEK DATA ON LPV/r PELLETS IN 990 CHILDREN IN RESOURCE-LIMITED SETTINGS

**Dalton C. Wamalwa**[1], Victor Musiime[2], Adeodata R. Kekitiinwa[3], Juliet Mwanga-Amumpaire[4], Rachel N. Musoke[5], Joseph K. Mbuthia[6], Elizabeth Maleche-Obimbo[7], Winstone M. Nyandiko[8], Elizabeth A. Bukusi[9], Maja Weisser[10], Nzovu Ulenga[11], Mariama Diallo[12], Vishal Goyal[12], Alistair Swanson[12]
*[1]Department of Paediatrics and Child Health, University of Nairobi, Nairobi, Kenya, [2]Joint Clinical Research Centre, Kampala, Uganda, [3]Baylor College of Medicine Children's Foundation, Kampala, Uganda, [4]Epicentre, Mbarara, Uganda, [5]Children of God Relief Institute, Nairobi, Kenya, [6]Gertrude's Children's Hospital, Nairobi, Kenya, [7]University of Nairobi, Nairobi, Kenya, [8]Department of Child Health and Paediatrics*

- *Moi University, AMPATH and Moi Teaching and Referral Hospital, Eldoret, Kenya, [9]Centre for Microbiology Research, Kenya Medical Research Institute, Kisumu, Kenya, [10]Ifakara Health Institute, Ifakara, Tanzania, United Republic Of, [11]Management Development for Health, Dar es Salaam, Tanzania, United Republic Of, [12]Drugs for Neglected Diseases Initiative, Geneva, Switzerland*

**Background:** LPV/r-based regimens remain an important treatment for children living with HIV (CLHIV), with established safety and efficacy. LPV/r pellets are an alcohol-free, heat stable improvement on LPV/r liquid for CLHIV who cannot swallow tablets. Treatment outcome data from large cohorts of CLHIV in resource-poor settings are limited. LIVING (NCT02346487) addresses this data gap across pediatric age groups.

**Methods:** Effectiveness, safety and acceptability of LPV/r 40/10mg pellets given in combination with ABC/3TC or AZT/3TC dispersible tablets to CLHIV was assessed in field conditions in a single-arm phase IIIb study in Kenya, Uganda and Tanzania. Eligibility: CLHIV weighing 3 to <25kg; ARV naïve, on liquid LPV/r-based or failing NNRTI based ART. Dosing: twice daily by WHO weight bands. Clinical assessments: screening, Day 1, Week 4, 12, and 12-weekly thereafter. Acceptability: via caregiver questionnaire. Primary effectiveness composite endpoint: being alive and on study drug with HIV-1 RNA <1000 cp/mL at W48, analyzed in all children who received study drugs.

**Results:** 990/1003 children enrolled received study drugs. 814/990 received ABC/3TC. Baseline data are presented in Table 1. Median treatment duration 72.1w (IQR 48.3-96.1). W48: 683/990 (69%) met the primary effectiveness endpoint; 169 (17%) had VL ≥1000 cp/mL, 97 (10%) prematurely discontinued (15 deaths and 82 discontinuations), and 41 (4%) had missing W48 VL data. Of the 852 with VL data, 448 (53%) had VL <50 cp/mL, 656 (77%) <400 cp/mL, and 683 (80%) <1000 cp/mL. At 96w, 235/265 (89%) evaluable children had <1,000 cp/mL. 222 grade 3-4 AEs occurred in 138/990 (14%) children. Most frequent: malaria, pneumonia, gastroenteritis and anemia. 95 treatment-related AEs occurred in 75 (8%) children; most frequent was diarrhea (3%). 157 SAEs occurred in 88 children; only 1 (diarrhea; grade 3) assessed as treatment-related. 17 deaths reported (2 after Week 48), one treatment-related (child with anemia on AZT for 2 years before enrolment). On first and last assessment visits, 751/942 (80%) and 869/942 (93%) caregivers described pellets as easy/very easy to administer and 830/942 (88%) and 886/942 (94%) reported their children accepted pellets well.

**Conclusion:** LPV/r pellets plus ABC/3TC or AZT/3TC were well-tolerated, effective and well-accepted in a large CLHIV cohort, many <24 mo and with advanced disease, in East Africa. This combination remains a good treatment option for CLHIV, as an alternative 1st line or following failure on DTG-based ART.

**Table 1: Demographic and baseline characteristics – safety analysis set (n=990)**

| | Overall N=990 n (%) or median (IQR) |
|---|---|
| Female | 509/990 (51%) |
| Age (months) (N=987) | 36.0 (IQR 19.7 to 56.0) [range: 2.0 to 148.0] |
| Aged <24 months | 316/987 (32%) |
| Weight (kg) | 12 (9 to 15) |
| WHO weight-for-age z-score (N=969) | -1.2 (-2.1 to -0.5) |
| ART naïve | 93/988 (9%) |
| ART exposed | 895/988 (91%) |
| HIV-1 RNA viral load ($log_{10}$ copies/mL) (N=929) | 2.8 (1.6 to 4.7) |
| HIV-1 RNA viral load ≥100,000 copies/mL | 174/929 (19%) |
| CD4 cell count (cells/$mm^3$) (N=936) | 1,459 (986 to 1,995) |
| WHO classification of HIV-associated immunodeficiency: | |
| Advanced | 110/937 (12%) |
| Severe | 187/937 (20%) |

## 722 HIGH DRUG RESISTANCE AND NEED FOR ART CHANGE IN CHILDREN WITH VIRAL FAILURE IN KENYA

**Lisa Abuogi**[1], Patrick Oyaro[2], Katherine K. Thomas[3], Bhavna Chohan[3], Evelyn Brown[4], Enericah C. Kariuki[4], Bilaal S. Ahmed[1], James Wagude[5], Eunice Kinywa[6], Irene Mukui[7], Leonard Kingwara[8], Boaz Oyaro[9], Lisa M. Frenkel[3], Rena Patel[3]
*[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Health Innovations Kenya, Kisumu, Kenya, [3]University of Washington, Seattle, WA, USA, [4]University of Washington in Kenya, Nairobi, Kenya, [5]Department of Health, Siaya County, Siaya, Kenya, [6]Ministry of Health, Kisumu, Kenya, [7]Ministry of Health, Nairobi, Kenya, [8]National HIV Reference Laboratory, National Public Health Laboratory, Nairobi, Kenya, [9]Kenya Medical Research Institute-CDC, Kisumu, Kenya*

**Background:** Growing drug resistance (DR) in children living with HIV (CLHIV) on antiretroviral treatment (ART) threatens to undermine global HIV targets to achieve viral suppression and health outcomes for CLHIV with virologic failure (VF). We present DR testing results and outcomes among children with VF in the randomized controlled Opt4Kids trial.

**Methods:** CLHIV ages 1-14 years on ART were enrolled in the Opt4Kids study from five government facilities in Kisumu County, Kenya March to December 2019. Children were individually randomized 1:1 to control (standard-of-care) or intervention (point-of-care viral load testing every three months with targeted DR testing (DRT) for those with VF (> 1000 copies/ml]). A multidisciplinary clinical management committee (CMC) reviewed targeted DRT results and gave management recommendations. DR patterns are described and clinical outcomes compared by Fischer's exact test.

**Results:** A total of 704 CHIV were enrolled in the study with a median age 9 years (interquartile range [IQR] 7, 12) and median time on ART of 5.8 years (IQR 3.1, 8.6). Among 349 CHIV enrolled in the intervention arm, 89 (26%) had one or more episodes of viremia of which 84 (94%) had at least one DRT. All children with a DRT had DR mutations identified: 73(84%) had major DR; 70 (83%) NNRTI, 54 (64%) NRTI, 10 (12%) PI as well as 41 (49%) with dual class NRTI-NNRTI and 9 (11%) triple-class DR. The CMC recommended an ART regimen change for 38/84 (45%), and 35 (92%) of these changed regimens by end of study follow-up. Another 12 (14%) CHIV underwent ART regimen change per facility staff as part of the national programmatic transition to dolutegravir (DTG).The CMC did not recommend an ART regimen change for the remaining 34 CHIV, the majority of whom (29; 85%) were on protease inhibitor (PI)-based ART without any major PI DR. Excluding those with programmatic ART changes, the study viral suppression (VS) outcome at 12 months showed VS in 22/38 (58%) with recommendation to change ART and 11/34 (32%) without recommendation to change ART (p=0.0357). Additionally, ART-suppression was observed in 9/12 (75%) with programmatic switch to DTG.

**Conclusion:** Over 80% of CLHIV undergoing targeted DRT had major drug mutations detected and more than half required ART regimen change to address drug resistance and/or to optimize the regimen. Targeted use of DRT in CLHIV with VF may improve viral suppression, retention, and clinical outcomes.

**Table 1: Study outcomes of children undergoing DRT in intervention arm**

| | Total children with DRT results | Children changing ART due to programmatic transition to DTG | Children recommended to change ART after DRT review | Children without ART change recommendation after DRT review |
|---|---|---|---|---|
| 12-month viral load | N=84(%) | N=12(%) | N=38[1](%) | N= 34(%) |
| | | | | |
| Suppressed | 42 (50) | 9(75) | 22(58) | 11(32) |
| Not suppressed | 28 (33) | 3(25) | 11(29) | 14(41) |
| Lost to follow up | 9 (11) | 0(0) | 3(8) | 6(18) |
| Died | 1 (1) | 0(0) | 0(0) | 1(3) |
| Missing VL | 4 (5) | 0(0) | 2(5) | 2(6) |

[1] includes three children recommended to change ART who had not by study end
DRT- drug resistance test
DTG- dolutegravir

## 723 EBV AND CMV VIREMIA PREDICT INCREASED MORTALITY IN HOSPITALIZED CHILDREN WITH HIV

**Lasata Shrestha**[1], Irene Njuguna[1], Donghoon Lee[1], Elizabeth Maleche-Obimbo[2], Michael Boeckh[1], Emily R. Begnel[1], Daisy J. Chebet[3], Judith A. Onyango[3], Lisa Marie Cranmer[4], Meei-Li Huang[1], Barbra A. Richardson[1], Grace John-Stewart[1], Dalton C. Wamalwa[2], Jennifer Slyker[1]
*[1]University of Washington, Seattle, WA, USA, [2]University of Nairobi, Nairobi, Kenya, [3]Kenyatta National Hospital, Nairobi, Kenya, [4]Emory University, Atlanta, GA, USA*

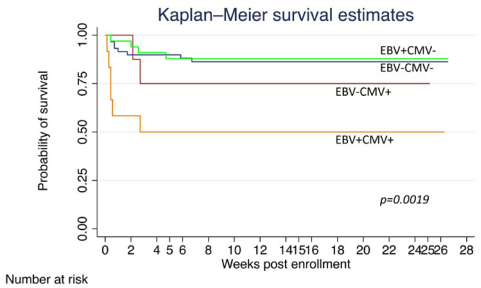
**Background:** We recently reported cytomegalovirus (CMV) levels >1000 IU/mL in plasma at hospital admission predicted a 74% higher risk of the combined endpoint of mortality or continued hospitalization at 15 days, and 5 days longer hospitalization in ART-naïve Kenyan children. Here, we examine Epstein-Barr virus (EBV) viremia as a predictor of outcomes in the same cohort, alone, and in synergy with CMV viremia.

**Methods:** The study was nested into the Pediatric Urgent Start of HAART study, which evaluated the benefit of accelerated ART for severely ill children diagnosed with HIV in hospital. CMV and EBV levels were measured in frozen plasma using qRT-PCR, with a limit of detection of 1 copy/reaction. Using a cutoff of 1000 copies/ml for EBV and 1000 IU/ml for CMV to define "viremia," we compared outcomes in children who were aviremic for both (CMV-EBV-), viremic for either CMV or EBV (CMV+EBV- or CMV-EBV+), and viremic for both (CMV+EBV+). We compared the risk of 6-month mortality and the combined endpoint using multivariable Cox and Poisson regression models, respectively,

adjusting for age and CD4%. Duration of hospitalization was compared between groups using the Mann-Whitney U test.

**Results:** Among 114 children, 53% were CMV-EBV-, 7% were CMV+EBV-, 30% were CMV-EBV+, and 11% were CMV+EBV+. CMV+EBV+ children at admission were relatively younger and had higher HIV RNA levels. The detection of CMV and EBV viremia, or level, were not significantly correlated. Compared to aviremic children, the crude risk of 6-month mortality was 5.31-fold greater in CMV+EBV+ viremic children (95%CI=1.84-15.4), and 3.39-fold (95%CI=1.14-10.2, p=0.03) greater after adjusting for CD4% and age. Viremia with only CMV (CMV+EBV-) or only EBV (CMV-EBV+) did not predict mortality, combined endpoint, or duration of hospitalization (p>0.05 for each). Compared against aviremic children, CMV+EBV+ viremic children had a 3.76-fold (95%CI=1.42-9.95, p=0.008) increased risk of 6-month mortality and 1.73 (95%CI=1.07-1.79, p=0.03) higher risk of combined endpoint after adjusting for CD4% and age. Duration of hospitalization was not significantly different for EBV+CMV+ survivors (Median=12 days [IQR=10, 16]) compared to aviremic children (Median=9 days [IQR=6, 15]), p=0.1).

**Conclusion:** Detection of concurrent CMV and EBV viremia at levels >1000/ml identified a subset of children with a very high risk of mortality, independent of age and CD4%. Determining whether this association is causal may inform novel interventions for this population.




## 724 PEDIATRIC AND ADOLESCENT RETENTION TRENDS ACROSS AGE BANDS DURING COVID-19 PANDEMIC

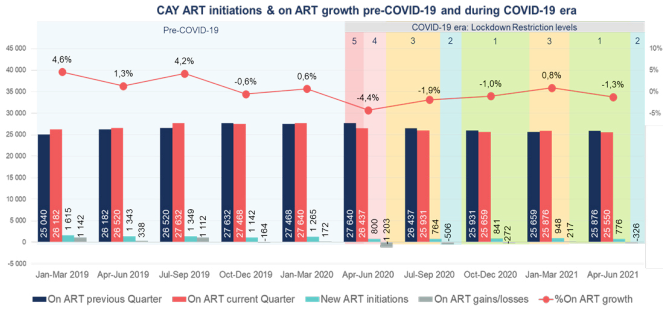
**Ziyanda T. Makaba**[1], Claire Serrao[1], Zamazamela P. Shelembe[1], Refilwe Mosome[1], Vimbainashe Sigauke[1], Dhirisha Naidoo[1]
[1]*BroadReach Corporation, Cape Town, South Africa*

**Background:** Progress towards the 90-90-90 HIV goals is slower for children, adolescents and youth ≤19 years (CAY) living with HIV, with only 71% of those knowing their status linked to sustained ART in the BroadReach supported districts. From the start of COVID-19 pandemic and lockdown, facility headcounts declined. We reviewed trends in CAY ART initiation and retention to evaluate effects of COVID-19 and lockdown on the already struggling CAY ART programme.

**Methods:** Retrospective data from October 2019 to June 2021 for CAY was analyzed. October 2019 to March 2020 data was categorised as pre-COVID and April 2020 to June 2021 as COVID-era. Indicators evaluated were ART initiations, remaining in care, lost to follow-up (LTFU) and returned to care. We analyzed trends disaggregated into age bands: <5, 5-9, 10-14 and 15-19 years.

**Results:** The quarterly ART initiation average was 1302 pre-COVID and 826 in COVID-era, (37% drop) with ages 5-9 and 10-14 years most affected (57% and 55% drop respectively). Pre-COVID CAY on ART growth was 10% (2% quarterly average). COVID-19 restrictions resulted in 8% decline in CAY on ART from 27640 to 25550 from January 2020 to June 2021. Ages 5-9 and 10-14 years had the largest attrition of -698 (15%) and -1209 (14%) respectively, with <5 years dropping by 16% (-326). However, ages 15-19 showed a gain of 143 adolescents (1% growth). Majority (66%) of CAY not in care were LTFU after being on ART >3 months, mostly noted from July to December 2020 (78%) with ages 5-9 and 10-14 years most affected (82% and 86% respectively). During more restrictive lockdown levels (April to June 2020), 4.4% CAY on ART were lost in one quarter vs 3.4% lost in the next 12 months (July 2020 to June 2021) of less restrictive levels; an average reduction of 0.85% per quarter. Intense tracing from May 2020 resulted in >94% CAY resuming treatment after more than a month of interruption vs the 17% resumption to interruption ratio seen in the 2 quarters prior.

**Conclusion:** COVID-19 pandemic and lockdown restrictions impacted negatively on an already poorly performing CAY ART program by reducing initiations and reversing gains made in retention. The worst affected age band was 5–14-year-olds which already had the largest performance gaps prior to the COVID-19 pandemic. As we continue to trace CAY back to care, we need to upscale interventions aimed at retention in care i.e., multi-month scripting and dispensing, HIV disclosure, community and differentiated ART delivery especially for the 5–14-year-olds.




## 725 IMPACT OF ECONOMIC EMPOWERMENT ON ART ADHERENCE IN HIV-POSITIVE ADOLESCENTS IN UGANDA

**Samuel Kizito**[1], Proscovia Nabunya[1], Flavia Namuwonge[2], Josephine Nabayinda[1], Joshua Kiyingi[1], Jennifer Nattabi[1], Fred Sewamala[1]
[1]*Washington University in St Louis, St Louis, MO, USA,* [2]*International Center for Child Health and Development, Masaka, Uganda*

**Background:** Optimal Antiretroviral Therapy (ART) adherence is associated with better treatment outcomes. However, ART adherence among adolescents living with HIV (ALWHIV) is low. Poverty remains a significant threat to ART adherence. There is scanty literature about the role of economic empowerment on ART adherence among ALWHIV. Also, ART adherence may be influenced through alternative mechanisms. We examined the mediation pathways for the association between an economic empowerment intervention and ART adherence among ALWHIV in Uganda.

**Methods:** In this longitudinal cluster-randomized controlled trial (2012 - 2018), we recruited 702 ALWHIV aged 12-16 in Uganda between January 2014 and December 2015. Thirty-nine clinics were randomized into the control (n=344) or intervention arm (n=358). The intervention comprised a long-term child development account (CDA), four micro-enterprise workshops, and 12 mentorship and educational sessions. We used Wilson's three-item self-report measure to determine ART adherence at baseline, 12-, 24-, 36- and 48-months post-intervention. We then used structural equation modeling (SEM) to test the mediation effect of mental health functioning, HIV stigma, family cohesion, food security, and stigma. We ran three separate models for adherence at 24-, 36-, and 48 months. Study is registered at ClinicalTrials.gov (#NCT01790373).

**Results:** At 24-months, the intervention directly improved ART adherence β=0.75 (95% CI: 0.03 – 2.52). Also, the intervention improved food security β=0.29 (95% CI: 0.05 - -0.53). While improved mental function, β= 0.001 (95% CI: 0.0004 – 0.002), and family cohesion β=0.09 (95% CI: 0.02 – 0.15) improved adherence. At 48 months, the intervention resulted in reduced stigma, β=-0.76 (95% CI: -1.38 - -0.13). While, stigma and low mental function reduced adherence, β=-0.12 (95% CI: -0.23 - -0.12) and β=-0.25 (95% CI: -0.42 - -0.08) respectively.

**Conclusion:** These results support the theory that economic empowerment improves patient key outcomes and demonstrate that financial savings and financial literacy are crucial in improving ART adherence. Therefore, there is a need to incorporate economic empowerment components in HIV care programs in low-income settings.

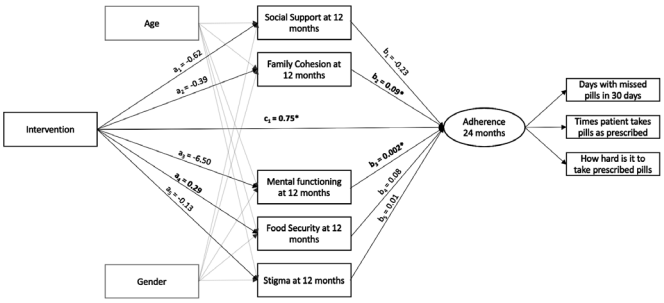



Figure 1: Structural equation model assessing the mediation pathways for the association between a family based economic empowerment intervention and adherence to antiretroviral therapy among adolescents living with HIV in Uganda.

## 726 ESTIMATING ATHEROSCLEROTIC RISK IN SOUTH AFRICAN YOUTH WITH PERINATALLY ACQUIRED HIV

**Sana Mahtab**[1], Lisa Frigati[2], Mothabisi Nyathi[1], Nana Akua Asafu-Agyei[1], Ntobeko Ntusi[1], Landon Myer[1], Heather Zar[1], Jennifer Jao[3]
*[1]University of Cape Town, Cape Town, South Africa, [2]Stellenbosch University, Tygerberg, South Africa, [3]Northwestern University, Chicago, IL, USA*

**Background:** Youth living with perinatally acquired HIV infection (YLPHIV) may be at higher risk of atherosclerotic cardiovascular disease (CVD) due to lifetime exposure to HIV and antiretroviral therapy (ART).
**Methods:** We determined the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) coronary arteries (CA) and abdominal aorta (AA) risk scores among YLPHIV and HIV-seronegative (HIV-) youth ≥15-years of age enrolled in the Cape Town Adolescent and Antiretroviral Cohort. Components of the PDAY score included: non-high-density lipoprotein (HDL) cholesterol ≥130mg/dL and HDL <40mg/dL], hyperglycemia (fasting plasma glucose ≥125mg/dL), hypertension (blood pressure ≥95th percentile for age, sex, and height), obesity (body mass index >30kg/$m_2$), and cigarette smoking (>1 pack/day in the past 3 months). Socio-demographics, viremia [categorized as sustained viremia (SV) = VL>50 copies/mL, transient viremia (TV) = mix of VL >50 and ≤50 copies/mL, or sustained virologic suppression (VS) = VL <50 copies/mL throughout the study], duration and type of ART were collected. Among YLPHIV, logistic regression was performed to assess factors associated with PDAY score >1 for CA and AA separately.
**Results:** Overall, 219 YLPHIV and 31 HIV- youth (median age 17 years) were included. Among YLPHIV, 8% had SV, and 54% had TV. Median duration on ART was 12 years; 57% of were on a nonnucleoside reverse transcriptase inhibitor–based ART while the rest received protease inhibitor-based ART. Among YLPHIV, 28% and 13% had a CA and AA PDAY score ≥1 respectively. High CA scores were attributed primarily to low levels of HDL cholesterol. Few YLPHIV met criteria for hypertension (2%, n=4) and hyperglycemia (0.5%, n=1). No HIV- youth had hypertension or hyperglycemia. More HIV- youth smoked than YLPHIV (16% vs 6%). SV [adjusted odds ratio (aOR)=15.7, p<0.01] and TV (aOR=2.4, p=0.03) compared to VS were associated with CA PDAY score >1 in YLPHIV. Duration of ART was also associated with a CA PDAY score >1 (aOR=1.1, p=0.04).
**Conclusion:** A substantial proportion of YLPHIV have PDAY scores reflecting increased aggregate atherosclerotic risk. Viremia and lifetime ART duration contribute to this risk, highlighting the importance of HIV control and monitoring cardiometabolic health as well as future studies to understand how ART impacts atherosclerotic risk in YLPHIV.

Table: Unadjusted and adjusted odds ratios for factors associated with PDAY scores ≥1 among YLPHIV

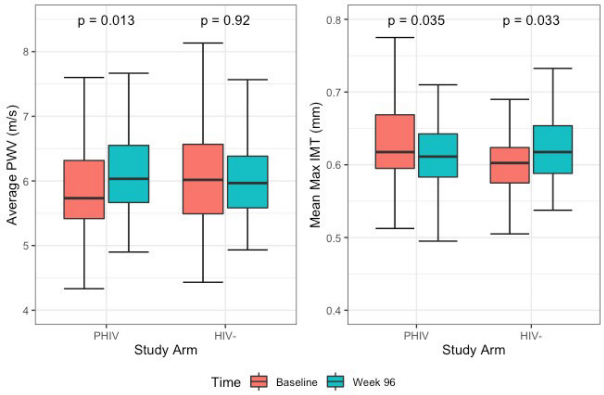
| Factor | Model for Coronary Artery PDAY score ≥1 | | | Model for Abdominal Aorta PDAY score ≥1 | | |
|---|---|---|---|---|---|---|
| | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | P value | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | P value |
| **Age at 48-month visit (years)** | 1.25 (0.96, 1.63) | 1.16 (0.86, 1.56) | 0.32 | 1.15 (0.82, 1.63) | 1.02 (0.70, 1.47) | 0.93 |
| **Sex** | | | | | | |
| Male | Ref | Ref | | Ref | Ref | |
| Female | 0.48 (0.26, 0.88) | 0.56 (0.29, 1.09) | 0.09 | 0.41 (0.18, 0.93) | 0.49 (0.21, 1.14) | 0.10 |
| **hsCRP (mg/L)** | 1.00 (0.98, 1.04) | 1.01 (0.98, 1.04) | 0.49 | 1.00 (0.96, 1.04) | 1.00 (0.96, 1.04) | 0.93 |
| **Viremia** | | | | | | |
| Sustained viral suppression | Ref | Ref | | Ref | Ref | |
| Transient viremia | 2.81 (1.36, 5.79) | 2.44 (1.08, 5.56) | 0.03 | 1.47 (0.59, 3.62) | 1.28 (0.46, 3.56) | 0.64 |
| Sustained viremia | 14.2 (4.2, 47.6) | 15.7 (3.94, 62.3) | <0.01 | 3.91 (1.09, 13.9) | 3.99 (0.87, 18.3) | 0.08 |
| **Duration on ART (years)** | 1.07 (0.97, 1.17) | 1.12 (1.01, 1.24) | 0.04 | 1.12 (0.98, 1.28) | 1.14 (0.99, 1.31) | 0.07 |
| **Current ART regimen** | | | | | | |
| 2 NRTI + NNRTI | Ref | Ref | | Ref | Ref | |
| 2 NRTI + PI | 2.13 (1.17, 3.87) | 1.11 (0.53, 2.29) | 0.79 | 1.75 (0.79, 3.85) | 1.11 (0.43, 2.86) | 0.82 |

ART, antiretroviral therapy; CI, confidence interval; hs-CRP, highly sensitive C-reactive protein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PDAY, Pathological Determinants of Atherosclerosis in Youth; PI, protease inhibitor; YLPHIV, youth living with perinatally acquired HIV.

## 727 LONGITUDINAL CHANGES IN SUBCLINICAL VASCULAR DISEASE IN UGANDAN YOUTH WITH HIV

**Sahera Dirajlal-Fargo**[1], Chenya Zhao[1], Abdus Sattar[1], Christine Karungi[2], Rashidah Nazzinda[2], Danielle Labbato[1], Nicholas Funderburg[3], Emmy Okello[4], Victor Musiime[2], Grace A. McComsey[1]
*[1]Case Western Reserve University, Cleveland, OH, USA, [2]Joint Clinical Research Centre, Kampala, Uganda, [3]The Ohio State University, Columbus, OH, USA, [4]Makerere University College of Health Sciences, Kampala, Uganda*

**Background:** The risk of cardiovascular disease (CVD) and prospective investigations in children and youth living with perinatally acquired HIV (PHIV) in sub-Saharan Africa are lacking. We investigated the progression of subclinical vascular disease in children with PHIV and uninfected (HIV-).
**Methods:** A prospective observational cohort study was performed in 101 PHIV and 97 HIV- from 2017-2021 at the Joint Clinical Research Center in Uganda. All participants were between 10-18 years of age. PHIVs were on ART with HIV-1 RNA level ≤400 copies/mL. Mean common carotid artery intima-media thickness (IMT) and pulse wave velocity (PWV) were evaluated at baseline and 96 weeks. Groups were compared using unpaired t test and potential predictors of IMT and PWV were assessed using quantile regression.
**Results:** Of the 198 participants recruited at baseline, 168 (89 PHIV, 79 HIV-) had measurements at 96 weeks. At baseline, median (Q1, Q3) age was 13 years (11,15) and 52% were females. At baseline median CD4+ cell counts were 988 cells/μL (638, 1308), median ART duration was 10 years (8, 11). At baseline, 85% had viral load < 50 copies/mL and remained undetectable at week 96. At baseline 72% were on an NNRTI based regimen, 53% of participants had a regimen switch between visits, 85% of whom switched to 3TC, TDF and DTG. PHIVs had higher monocyte and T-cell activation; higher sCD14 (p=0.01) and elevated frequencies of non-classical monocytes (p<0.001). At baseline, median IMT was slightly thicker in PHIVs compared to controls (p<0.01), while PWV did not differ between groups (p=0.08). At week 96, PWV increased in PHIV (by 0.3 m/s, p=0.01) but did not significantly change in HIV- (p=0.92); IMT decreased in PHIV (p=0.03) and increased in HIV- (p=0.03;, Figure). PWV and IMT were not different between the groups at 96 weeks (p≥0.37). In univariate analyses, CD8+ activated T cells at baseline (r=0.25, p=0.02) correlated with IMT in PHIV, however, in quantile regression, after adjusting for demographic variables only BMI remained associated with IMT (p=0.03). In longitudinal analyses in PHIV, after adjusting for age, sex, BMI, and CD4 nadir, abacavir use was associated with greater IMT (β=0.71, 95%CI 0.041,0.082, p=0.05).
**Conclusion:** Higher IMT was found in Ugandan PHIV, however viral suppression may prevent progression, while larger BMI and prolonged use of abacavir may increase subclinical vascular disease. Longer follow-up is required to understand the downstream clinical implications of our findings.




## 728 MENTAL HEALTH AND TREATMENT OUTCOMES IN ADOLESCENTS LIVING WITH HIV IN WEST AFRICA

**Désiré Lucien Dahourou**[1], Marc Harris Dassi Tchoupa Revegue[2], Marie-Sylvie N'Gbeche[3], Caroline Yonaba[4], Corinne Moh[5], Kouakou Kouadio[6], Patricia Nindjin[6], Karen Malateste[7], Jean-Claude Azani[8], Julie Jesson[2], Eulalie Kangah[8], Elisabeth Thio[9], Philippe Msellati[8], Valériane Leroy[2]
*[1]Institut de Recherche en Sciences de la Santé, Ouagadougou, Burkina Faso, [2]INSERM, Toulouse, France, [3]CePReF, Abidjan, Cote d'Ivoire, [4]Université Joseph Ki-Zerbo, Ouagadougou, Burkina Faso, [5]CePReF, Abidjan, Cote d'Ivoire, [6]CiRBA, Abidjan, Cote d'Ivoire, [7]Université de Bordeaux, Bordeaux, France, [8]Programme ANRS-*

*PACCI, Abidjan, Cote d'Ivoire, [9]Centre de Recherche Internationale pour la Santé, Ouagadougou, Burkina Faso*

**Background:** Mental health comorbidities such as depression and anxiety are prevalent among people living with HIV. However, data on mental health in adolescent living with HIV (ALHIV) are limited, particularly in West Africa. We studied the prevalence of depression and anxiety in association with antiretroviral treatment (ART) outcomes in ALHIV at inclusion in the OPTIMISE-AO trial in Burkina Faso and Cote d'Ivoire.

**Methods:** OPTIMISE-AO-ANRS-12390 is a stepped-wedge trial aimed to improve HIV-disclosure and treatment adherence in ALHIV aged 10-17 years, in six paediatric clinics in four countries (Burkina Faso, Côte d'Ivoire, Mali, Togo) nested within the IeDEA-WA cohort. At inclusion, depression and anxiety were assessed using the Patient Health Questionnaire-9 (PHQ-9), and the General Anxiety Disorder-7 (GAD-7), respectively. Using a logistic regression, we identified factors associated with depression or anxiety combined and with viral suppression (VS: viral load<50cp/mL) at inclusion.

**Results:** From February to October 2021, 317 ALHIV were enrolled at a median age of 14 years (interquartile range: 12–16), 85% were >12 years, 52% were female, 30% at WHO clinical stage 3/4; 74% were treated with a Dolutegravir (DTG) based regimen. DTG regimen was more commonly used in Burkina Faso (90%) compared to Cote d'Ivoire (66%). At inclusion, 41% were fully HIV-disclosed (defined when the adolescent names his/her illness as HIV/AIDS). Overall, 34% of ALHIV had mild to moderate depression or anxiety. Prevalence of mild-moderate depression and of mild anxiety were 30% and 20%, respectively. Adjusted for gender, age and having other siblings living with HIV, ALHIV not fully HIV-disclosed to (adjusted Odds Ratio [aOR]: 2.50, 95% Confidence Interval [95%CI]: 1.41-4.43) and enrolled in Cote d'Ivoire (aOR: 8.94, 95%CI: 4.16-19.19) were at higher risk of depression or anxiety. At inclusion, 78% were in VS regardless of their ART regimen. Adjusted for gender, ALHIV with mild to moderate depression or anxiety (aOR: 0.27, 95%CI: 0.13-0.59) and those enrolled in Burkina Faso (aOR: 0.30, 95%CI: 0.14-0.65) were significantly less likely to be in VS.

**Conclusion:** In these West-African ALHIV cohorts, ALHIV were mainly switched on DTG regimen, but VS remains suboptimal and worsened by mental health conditions. Tailored interventions are urgently needed to address both depression or anxiety and ART treatment adherence among West African ALHIV.

## 729 MENTAL HEALTH DISORDERS IN HIV-POSITIVE ADOLESCENTS AND YOUTHS: DATA FROM MOZAMBIQUE

New Investigator Scholar

**Francesco Di Gennaro**[1], Anton Pozniak[2], Claudia Marotta[3], Lucy Ramirez[4], Hamilton Cardoso[4], Vasco Cinturao[4], Natalia Chimundi[4], Andrea Atzori[3], Izilda Chaguruca[4], Francesca Tognon[3], Giovanna De Meneghi[4], Edson Namarime[4], edoardo Occa[4], Giovanni Putoto[3], Annalisa Saracino[5]

*[1]University of Bari, Bari, Italy, [2]Department of HIV Medicine, Chelsea & Westminster Hospital NHS Foundation Trust, London, UK, London, UK, [3]Doctors with Africa CUAMM, Padua, Italy, [4]Doctors with Africa CUAMM, Beira, Mozambique, [5]Clinic of Infectious Diseases, University of Bari, University Hospital Policlinico, Bari, Italy*

**Background:** Adolescent mental health is a significant public health concern, which is extremely relevant when referring to adolescents living with HIV. Adolescence is a critical phase of physical, emotional and social changes, which may impact adherence to HIV care and ART. Mozambique has contemporary 52% of its population aged under 18y and the world's 8th highest HIV prevalence. Notably, 120,000 HIV-positive adolescents live in the country. In order to better understand the proper intervention to deliver, we performed an observational study to evaluate anxiety, depression, post-traumatic stress disorder and alcohol-drug abuse in adolescents and youth assessing health services in Beira district, Mozambique.

**Methods:** From 20 November 2019 to 20 October 2021, all adolescents and youth (10-24y) accessing one of the psychological services offered at 8 Servicios Amigos dos Adolescentes (SAAJ) of the Beira District, were screened by a trained psychologist using the following standardized tools: GAD-7 for anxiety, PHQ-9 for depression, PC-PTSD-5 for post-traumatic stress disorder, CAGE-AID for alcohol -drug abuse. Data from the psychological consultation were recorded on an open-source platform (Kobo Tool). HIV positive and negative subjects were compared and characteristics potentially associated with anxiety status (GAD-7>10), depression (PHQ-9 ≥11), post-traumatic stress disorder (PTSD-5 ≥3) and substance abuse (CAGE ≥2) were evaluated using a multivariable logistic regression model.

**Results:** Overall, 2,108 adolescents and youth were included in the study (63% F, median age: 19 years [IQR:16-21]). Of them, 1096 (52%) were HIV positive. HIV positive adolescent had worst scores of all the four tools tested and for concomitant MH disorders (GAD-7, PHQ-9, PTSD-5 and CAGE). The multivariable logistic regressions showed a greater probability to be GAD-7>10 for women vs men [(AOR): 1.46, 95% CI: 1.01-2.10, p-value=0.042], and for people HIV+ vs negative (AOR: 1.78, 95%CI 1.25-2.54, p-value<0.01). Higher values of CAGE (≥2) and PTSD (≥ 3) seemed to be associated only with HIV positive condition (AOR:4.87, 95%CI: 3.72-6.38, p-value<0.01 and AOR:1.73, 95%CI: 1.28-237, p-value<0.01, respectively)

**Conclusion:** HIV positive adolescent and youth had the worst scores of all the administered mental health screening tools. According to our results, public health policies and intervention targeted to the metal health of this fragile group should be addressed with priority.

**Table 3 Questionnaires by HIV status and total**

| | HIV - N=877 (48%) | | HIV + N=934 (52%) | | Total N=1811 | | p-value* |
|---|---|---|---|---|---|---|---|
| Generalized Anxiety Disorder- 7 (GAD-7) (median and IQR) | 3 | 1-6 | 6 | 4-9 | 5 | 2-8 | <0.01 |
| Gad-7 >=10 (n and %) | 67 | 7,6 | 96 | 10,3 | 163 | 9 | 0,059 |
| PHQ-9 Depression (median and IQR) | 3 | 1-5 | 5 | 3-7 | 4 | 2-6 | <0.01 |
| PHQ-9 Depression>=11 (n and %) | 67 | 7,6 | 106 | 7,1 | 133 | 7,3 | 0,023 |
| PTSD-5 (Post Traumatic Stress Disorder) (median and IQR) | 0 | 0-1 | 1 | 1-2 | 1 | 0-2 | <0.01 |
| PTSD-5 >=3 (n and %) | 82 | 9,4 | 137 | 14,7 | 219 | 12,1 | 0,001 |
| CAGE Substance Abuse (Alcohol and Drugs) (median and IQR) | 0 | 0-1 | 1 | 1-2 | 1 | 0-1 | <0.01 |
| CAGE >2 (n and %) | 88 | 10,0 | 334 | 35,8 | 422 | 23,3 | <0.01 |

Note: *Fisher exact test or Mann-Whitney test, as appropriated

## 730 PREVALENCE OF NONALCOHOLIC FATTY LIVER DISEASE VERTICALLY HIV-INFECTED YOUTHS

**Itziar Carrasco**[1], María Luisa Navarro[1], Sonia Alcolea[2], Antonio Olveira[2], Angel Lancharro[1], Maria Luisa Montes[2], Cristina Díez[1], Luis Escosa[2], Maria Jose Mellado[2], Carmen Busca Arenzana[2], Talia Sainz[2]

*[1]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Hospital La Paz Institute for Health Research, Madrid, Spain*

**Background:** The prevalence of subclinical liver abnormalities is high among people living with HIV, but data regarding perinatally HIV-infected children and adolescents (PHIV) are scarce. Non-invasive image techniques offer an opportunity to address non-alcoholic fatty liver disease (NAFLD) in a population in which the scores validated for adults have not been tested.

**Methods:** Prospective transversal study including PHIV under follow-up at the Spanish National Cohort of HIV-infected children and adolescents (CoRISpe) and HIV-exposed uninfected siblings as controls. Non-invasive imaging techniques for the diagnosis of NAFLD and/or fibrosis were performed, including Shear Wave Elastography, Fibroscan and Controlled Attenuation Parameter (CAP). Anthropometric measurements and biochemistry including lipid profile were performed, and four scores to predict NAFLD/fibrosis were calculated and their accuracy evaluated.

**Results:** Seventy-six participants (59.2% women) with a median age of 19 years [IQR: 15.5 – 25.6] were included, 38 were PHIV and 38 age and sex-matched controls. All HIV participants were on ART, their immunological situation was good and 86.8% were virologically suppressed. The prevalence of NAFLD by non-invasive imaging techniques was 28.9% in PHIV vs. 7.9% among non-HIV infected controls (p=0.02). The performance of scores based on clinical and analytical parameters was very poor. Participants with NAFLD had a significantly higher BMI, but only 27.3% presented overweight. Differences in HIV-related parameters between the groups were non-significant, except for the CD4/CD8+ T-cells ratio, decreased among PHIV diagnosed with NAFLD (p=0.04).

**Conclusion:** The prevalence of NAFLD was high (28.9%) among PHIV, and only partially explained by overweight and metabolic syndrome defining factors. The scores based on clinical and analytical parameters did not accurately identify subjects at risk. Therefore, liver ultrasound assessment should be considered for the screening of NAFLD among PHIV in routine clinical practice.

| Parameters | PHIV (n=38) | HIV-negative controls (n=38) | *p-value* |
|---|---|---|---|
| Age, y | 18.0 (14.9 - 24.2) | 22.7 (15.4 - 27.6) | 0.16 |
| Women (%) | 22 (57.9) | 23 (60.5) | 0.82 |
| Origin (%)<br>Spain<br>Latinamerica<br>Sub Saharan Africa<br>Asia | <br>24 (63.2)<br>5 (13.2)<br>8 (21.1)<br>1 (2.6) | <br>32 (84.2)<br>4 (10.5)<br>0 (0.0)<br>2 (5.3) | **0.02** |
| Weight, kg | 54.0 (44.6 – 60.3) | 60.7 (48.9 – 72.3) | **0.04** |
| Height, cm | 158.0 (152.0 – 168.0) | 169.3 (152.9 – 180.0) | **0.02** |
| BMI | 20.3 (18.4 – 23.6) | 22.0 (19.4 – 23.5) | 0.27 |
| Overweight (BMI > 25) | 6 (15.8) | 5 (13.2) | 0.74 |
| Waist, cm | 71.0 (65.0 – 77.0) | 75.3 (68.1 – 81.0) | 0.25 |
| Hip, cm | 87.5 (79.0 – 90.8) | 90.0 (77.1 – 94.0) | 0.44 |
| Waist-hip ratio | 0.86 (0.79 – 0.91) | 0.87 (0.83 – 0.92) | 0.57 |
| NAFLD diagnosis by imaging techniques (%) | 11 (28.9) | 3 (7.9) | **0.02** |
| Fibrosis (%) | 3 (7.9) | 0 (0) | 0.21 |
| FibroScan result, KPa | 5.0 (4.2 – 5.6) | 4.1 (3.6 – 5.1) | **0.01** |

## 731 WEIGHT GAIN AMONG ADOLESCENTS ON DOLUTEGRAVIR: A REAL CONCERN?

**Jesus Riscart**[1], Eva Soria[2], Luis Prieto[3], Luis Escosa[1], Claudia Fortuny[4], Dolores Falcon[5], Antoinette Frick[6], Jose Tomas Ramos Amador[7], Matilde Bustillo[8], Maria Penin[9], Pilar Collado[8], María Luisa Navarro[10], Santiago Jiménez de Ory[10], Talia Sainz[1]

*[1]Hospital La Paz Institute for Health Research, Madrid, Spain, [2]Universidad Autónoma de Madrid, Madrid, Spain, [3]Hospital Universitario 12 de Octubre, Madrid, Spain, [4]Hospital Sant Joan de Déu Barcelona, Esplugues, Spain, [5]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [6]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [7]Hospital Universitario Clínico San Carlos, Madrid, Spain, [8]Hospital Universitario Miguel Servet, Zaragoza, Spain, [9]Hospital Universitario Príncipe de Asturias, Madrid, Spain, [10]Hospital General Universitario Gregorio Marañón, Madrid, Spain*

**Background:** Integrase Inhibitors (INI) are now the first-line treatment for people living with HIV, including children. Clinical trials among adults have risen concerns regarding weight gain in patients starting or switching to INI. Clinical trials in children and adolescents are ongoing, as there is concern regarding weight gain in this population, characterized by important changes in body composition. We aim to describe anthropometric evolution of children and adolescents on INI versus other regimens.

**Methods:** Within the Spanish Cohort of Pediatric HIV, patients below 24 years of age started on or switched to a dolutegravir containing regimen up to December 2019 and with at least 12 months follow-up data were included in the study. A control group of patients not receiving INI was recruited from the same cohort. Anthropometrics were collected every 6 months for up to 24 months of follow-up. The 2010 Spanish growth charts were used to estimate BMI-Z-Score.

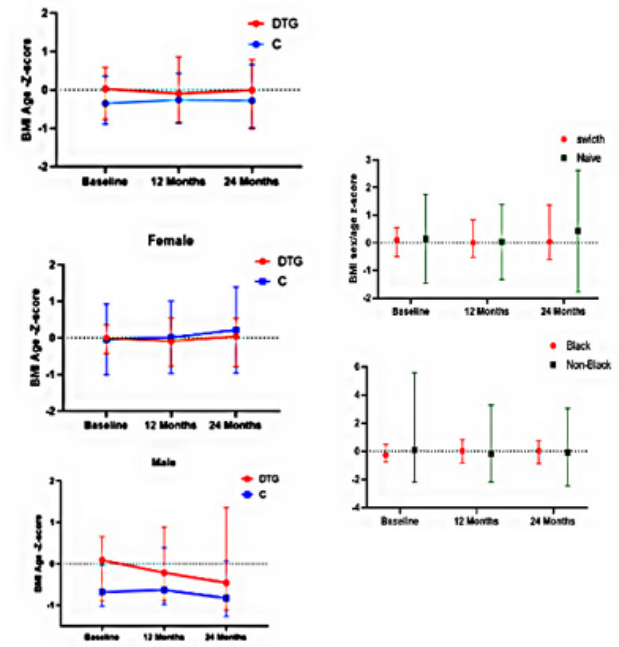
**Results:** A total of 179 patients were included, 66.3% female, 54.2% Caucasian, with a median age of 14 years (12.0 -17.3). Among the 83 patients on dolutegravir, 62.1% corresponded to treatment switch and treatment regimen included abacavir plus lamivudine in 80%. In the control group, treatment was based on efavirenz (35%), protease inhibitors (26%) or elvitegravir (35%), mostly combined with tenofovir-alafenamide fumarate (TAF) (43%), abacavir/lamivudine (28%) or tenofovir (17%). Both groups were comparable regarding age, gender distribution, ethnicity, BMI at baseline and CDC stage. The median follow-up was 20.7months [17.1- 22.9]. Over follow-up, no significant increase in weight z-score and/or BMI was observed. Sensitivity analysis by gender and ethnicity did not show differences either, as shown in Figure 1.

**Conclusion:** In this cohort study including children and adolescents, no association between exposure to dolutegravir and weight gain was found. Although these data are reassuring, larger studies and longer follow-up are needed in order to address the long-term effects of dolutegravir on weight during the unique period of adolescence.

TABLE 1. Characteristics of Children at baseline at Dolutegravir and non-Dolutegravir Regimens.

| | Antiretroviral Regimen | | P |
|---|---|---|---|
| | Dolutegravir (N=83) | Non-Dolutegravir (N=83 ) | |
| Demographic data | | | |
| Age at inclusion† (years) | 14,52 (11,94 - 17,41) | 14,82 (12.1 - 17.1) | 0.85 |
| Female / Male (%) | 55(66.3) / 28 (33.7) | 55 (66.3) / 28 (33.7) | 0,35 |
| Ethnicity (%) | | | |
| Caucasian | 39 (46.8) | 50 (60.2) | 0.212 |
| Black | 26 (31.3) | 24 (28.9) | |
| Latino | 11 (13.2) | 6 (7.2) | |
| Gypsy | 3 (3.6) | 1 (1.2) | |
| North-Africa (Magreb) | 3 (3.6) | 1 (1.2) | |
| Asian | 1 (1.2) | 1 (1.2) | |
| Country of birth (%) | | | |
| Spain | 61 (73.5) | 60 (72) | 0.231 |
| Abroad | 22 (26.5) | 23 (28) | |
| HIV-related parameter | | | |
| Vertical HIV Transmission (%) | 83 (100) | 83 (100) | - |
| Age at diagnosis† (years) | 0.57 (0.19 – 2.09) | 0.50 (0.14 – 2.17) | 0.988 |
| CDC clinical stage (%) | | | |
| A | 35 (42.2) | 38 (45.8) | 0.528 |
| B | 30 (36.1) | 27 (33.3) | |
| C | 16 (19.3) | 16 (18.7) | |
| Unknown | 2 (2.4) | 2 (2) | |
| VL (copies/mL)† | 50 [0 - 1100] | 80 [10 - 2000] | 0.745 |
| VL< 50 copies/mL N (%) | 56 (67) | 45 (55) | 0.354 |
| Naive patients N (%) | 27 (33) | 38 (45) | 0.354 |
| Total CD4 count (cell/mcL) | 531 (300- 721) | 510 (298 - 697) | 0.457 |
| CD4 T cell count (%) | 21.3 (13.4 - 27) | 20.8 (12.1 – 26.8) | 0.25 |
| ART Regimens (%) | | | |
| ABC + 3TC + DTG | 66 (80) | NA | |
| FTC + TDF + DTG | 5 (6) | NA | |
| DRV + DTG | 12 (14) | NA | |
| FTC + TAF + DRV + Cob | NA | 20 (24) | |
| FTC + TAF + RPV | NA | 18 (22) | |
| 3TC + ABC + EFV | NA | 17 (20) | |
| FTC + TDF + EFV | NA | 14 (17) | |
| AZT + ABC + KLT | NA | 14 (17) | |

†Expressed as median (IQR).
3TC: lamivudine; ABC: abacavir; AZT: Azidothymidine; Cob: cobicistat; DRV: Darunavir; DTG, dolutegravir; EFV: efavirez; FTC: emtricitabine; HIV: human immunodeficiency virus; IQR: interquartile range; KLT: lopinavir/r. NA: not applicable; TDF: tenofovir disoproxilfumarate. RPV: rilpivirine; TAF: tenofovir alafenamide; VL: Viral load. ZDV: zidovudine.



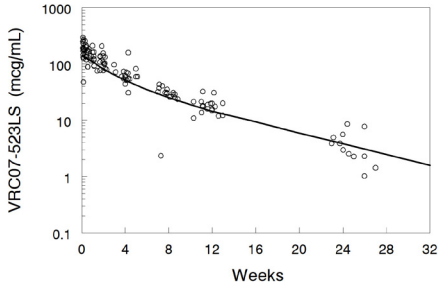

## 732 EXTENDED SAFETY AND PK OF ANTI-HIV MONOCLONAL Ab VRC07-523LS IN HIV-EXPOSED INFANTS

**Coleen K. Cunningham**[1], Edmund Capparelli[2], Elizabeth J. McFarland[3], Petronella Muresan[4], Charlotte Perlowski[5], Dwight E. Yin[6], Jack Moye[7], Sai Majji[7], Lynette Purdue[6], Paul A. Harding[3], Adrian McDermott[6], John R. Mascola[6], Barney

S. Graham[6]
*[1]University of California Irvine, Irvine, CA, USA, [2]University of California San Diego, San Diego, CA, USA, [3]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [4]Statistical and Data Analysis Center/Frontier Science and Technology Research Foundation, Boston, MA, USA, [5]FHI 360, Durham, NC, USA, [6]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [7]National Institute of Child Health and Human Development, Bethesda, MD, USA*

**Background:** Vertical HIV-transmission continues to occur due to barriers to antiretroviral therapy (ART). Prevention of infection might be improved with a potent, broadly neutralizing, monoclonal antibody (bNAb) administered to exposed infants. VRC07-523LS is 5-fold more potent and has a prolonged $T_{1/2}$ compared to VRC01 and may provide protective levels over the duration of breastfeeding.
**Methods:** This is an open label study of VRC07-523LS administered to HIV-exposed infants at increased risk of HIV infection. Formula-fed infants receive 80 mg subcutaneous (SC) within 72 hrs of birth (Cohort 1) and breast-fed infants receive 80mg SC within 5d of birth and 100 mg SC at week 12 (Cohort 2) if still breastfeeding. Infants and their mothers also receive ART to prevent HIV transmission. Infant safety assessments and VRC07-523LS levels are collected out to 24 weeks. The target week 12 (C12wk) level is 10 mcg/mL: the level needed to neutralize >90% of tier II viruses in a multiclade panel.
**Results:** Infants in Cohorts 1 (N=11; 4 US sites) and 2 (N=11; 2 African sites) received 80mg VRC07-523LS as a single SC injection at a median of 1 and 4d after birth, respectively, resulting in an average dose of 26 mg/kg (range 18-35 mg/kg). Enrollees were 59% male, 86% Black, and 9% Hispanic. Three in Cohort 2 did not receive week 12 dose, 2/3 due to cessation of breastfeeding. VRC07-523LS was well tolerated. In Cohort 1, 1 infant had injection site erythema of 0.5cm and 1 had tenderness (Grade 1). In Cohort 2, every infant had a local reaction after each injection. Most local reactions were Grade 1; but 3/11 and 2/8 infants had Grade 2 induration after dose 1 and 2, respectively. Most (76%) local reactions resolved within 24 hrs. All ≥Grade 3 events within 30 days of VRC07-523LS occurred after dose 1: 4 infants in Cohort 1 (vomiting [N=2], neutropenia, parainfluenza sepsis); and 1 infant in Cohort 2 (sepsis), none related to study treatment. $C_{max}$, $T_{max}$, and C12wk were 203±48 mcg/mL, 1.8±1.6 d, and 16.7+6.8 mcg/mL. $T_{1/2}$ was approximately 34d, similar to adults, but C12WK levels were lower than adults, suggesting infant SC bioavailability <1. Growth contributed to the fall in VRC07-523LS concentration, but levels remained over the target of 10 mcg/mL at week 12 (figure).
**Conclusion:** SC VRC07-523LS is safe and well-tolerated when administered to neonates. VRC07-523LS, with its enhanced potency, rapid absorption, and slow elimination, can quickly achieve and maintain target levels with dosing every 3 months.

Figure: VRC07-523LS plasma concentrations post first dose




## 733 SUBOPTIMAL LOPINAVIR EXPOSURE ON 8-HOURLY LPV/r 4:1 IN HIV/TB-COINFECTED CHILDREN

**Chishala Chabala**[1], Anna Turkova[2], Monica Kapasa[3], Kristen C. Lebeau[2], Kevin M. Zimba[3], Lubbe Wiesner[4], Khozya D. Zyambo[3], Louise C. Choo[2], Chalilwe Chungu[3], Joyce C. Lungu[3], Angela M. Crook[2], Veronica Mulenga[3], Diana Gibb[2], Helen McIlleron[4]
*[1]University of Zambia, Lusaka, Zambia, [2]Medical Research Council, London, UK, [3]University Teaching Hospital, Lusaka, Zambia, [4]University of Cape Town, Cape Town, South Africa*

**Background:** Young children with HIV/TB co-infection have limited antiretroviral treatment (ART) options. Lopinavir/ritonavir 4:1 (LPV/r) is widely used for first- and second-line ART but lopinavir (LPV) exposures are profoundly reduced by concomitant rifampicin. Recommended super-boosted lopinavir (LPV/r 1:1) is not feasible, as single-entity ritonavir is not widely available. A previous study in 11 children showed that 8-hourly liquid LPV/r formulation co-administered with rifampicin achieved targeted trough concentrations of LPV ≥1 mg/L in nearly two-thirds of children, suggesting that higher LPV/r dosing could potentially be used. We evaluated increased 8-hourly LPV/r (4:1) doses in HIV/TB co-infected children in a substudy of the SHINE trial (ISRCTN 63579542).
**Methods:** HIV/TB co-infected Zambian children, weighing 3.0 to <20 kg, on LPV/r-based ART and rifampicin-containing TB treatment, received liquid LPV/r 4:1 formulation 8-hourly using weight band (WB) dosing 31-40 and 20-22 mg/kg in the lowest and highest WBs, respectively. Children were switched to WHO-recommended 12-hourly LPV/r 2 weeks after stopping rifampicin. LPV plasma concentrations were assessed on 8-hourly LPV/r and repeated 2 weeks after returning to 12-hourly dosing. Samples were obtained pre dose and post dose at 1, 2, 4, 6 and 8hr, as well as 12 hr on 12-hourly dosing.
**Results:** 15 children (10[66%] males) with a median age of 3.0 (range 1.0 to 7.0) years were enrolled and received median LPV 23(range 21-37) mg/kg/dose. Plasma LPV exposures on 8-hourly LPV/r with rifampicin were lower compared to 12-hourly dosing (AUC24 GMR [90% CI] 0.35[0.21-0.61]) (Table). Only 7/15(44.7%) and 8/12(66.7%) children achieved LPV Cmin ≥1mg/L post dose trough concentrations (8hr and 12hr) with and without rifampicin respectively. During median 12 (IQR 4-16) weeks on 8-hourly LPV/r, 2 patients had 3 grade 3/4 adverse events (2 pneumonias, 1 urinary tract infection) deemed unrelated to the intervention; there were no treatment-related discontinuations.
**Conclusion:** LPV/r oral solution given in increased doses 8-hourly alongside rifampicin did not reach adequate LPV concentrations, and therefore unsuitable for HIV/TB co-infected children. The subtherapeutic exposures observed after TB treatment raise questions about the bioavailability of LPV/r oral solution in this population and supports the rapid transition to dolutegravir-based ART.

**Table: Patient characteristics and pharmacokinetic measures**

| Patient characteristics | LPV/r 8-hourly during TB treatment, N=15 | LPV/r 12-hourly after TB treatment, N=12 | p-value |
|---|---|---|---|
| | | | |
| Age in years, median (IQR) | 3.2 (2.3, 4.3) | 4.0 (2.6, 4.7) | - |
| Sex, male | 10 (67) | 7 (58) | - |
| WHZ, median (IQR) | 0.2 (-0.7, 0.9) | 0.0 (-0.2, 1.3) | p=0.79 |
| | | | |
| **Pharmacokinetic measures** | n=15 | n=12 | GMR (90% CI) |
| $AUC_{24}$, median (IQR), mg.hr/L | 55.32 (5.61, 222.18) | 121.63 (35.85, 353.81) | 0.35 (0.21, 0.61) |
| $C_{max}$, median (IQR), mg/L | 3.04 (0.62, 12.70) | 9.45 (3.03, 17.70) | 0.39 (0.24, 0.64) |
| $C_{min}$, median (IQR), mg/L | 0.90 (0.04, 4.39) | 3.03 (0.54, 9.39) | 0.35 (0.30, 0.83) |
| $C_{min}$ ≥1mg/L, n (%) | 7 (46.7) | 8 (66.7) | p=0.44 |

LPV/r; Lopinavir/ritonavir, WHZ; weight-for-height z-score, GMR; geometric mean ratio with 90% confidence interval (calculated from 12 paired observations); $AUC_{24}$; area under the concentration-time curve from time 0 to 24 hours (calculated using 3 x $AUC_{8hr}$ and 2 x $AUC_{12hrs}$), $C_{max}$; peak plasma concentration, $C_{min}$; 8 or 12 h trough concentration for the respective 8- and 12-hour dosing intervals.

## 734 TAF/TFV PHARMACOKINETICS WHEN GIVEN WITH PI/InSTI ART IN THE CHAPAS-4 PEDIATRIC TRIAL

New Investigator Scholar

**Hylke Waalewijn**[1], Alexander Szubert[2], Lubbe Wiesner[3], Chishala Chabala[4], Mutsa Bwakura-Dangarembizi[5], Shafic Makumbi[6], Joan Nangiya[7], Vivian Mumbiro[5], Veronica Mulenga[4], Victor Musiime[7], David M. Burger[1], Diana Gibb[2], Helen McIlleron[3], Angela Colbers[1]
*[1]Radboud University Medical Center, Nijmegen, Netherlands, [2]MRC Clinical Trials Unit at University College London, London, UK, [3]University of Cape Town, Cape Town, South Africa, [4]University Teaching Hospital, Lusaka, Zambia, [5]University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe, [6]Joint Clinical Research Centre, Mbarara, Uganda, [7]Joint Clinical Research Centre, Kampala, Uganda*

**Background:** Tenofovir alafenamide fumarate (TAF) is a prodrug of tenofovir (TFV) and compared to tenofovir disoproxil fumarate (TDF) causes less renal and bone toxicity. Pharmacokinetic (PK) data on the use of TAF with boosted protease inhibitors (PIs) and dolutegravir (DTG) in children is currently lacking. We undertook nested PK substudies in the CHAPAS4 randomized controlled trial (#ISRCTN22964075) evaluating practical TAF dosing in weight bands combined with one of 3 boosted PIs or DTG.
**Methods:** 919 African children aged 3-15 years failing first-line ART were randomised to TAF versus standard of care (SOC: abacavir or zidovudine) and to DTG, atazanavir/r (ATV/r), darunavir/r (DRV/r) or lopinavir/r (LPV/r) in a factorial design and are being followed for 96 weeks. Children taking TAF/emtricitabine weighing 14-25kg and >25kg took 15/120mg and 25/200mg respectively,

regardless of third drug in the combination. At steady state, an 8- to 9-sample (T=0, [0.5,] 1, 2, 4, 6, 8, 12, 24 hours after dose) PK curve was constructed for each child in the PK substudy. TAF and TFV plasma concentrations were measured using a validated LC-MS/MS method. Geometric mean (GM) AUC and $C_{max}$ were calculated for TAF and TFV and compared to reference parameters of adults taking 25mg TAF with/without a boosted PI. Relative to adults, we aimed for comparable or higher TAF AUC (206.4 ng*h/mL) for efficacy while ideally staying below TFV AUC of 937 ng*h/mL as a target for safety.

**Results:** 104 children from Uganda, Zambia, and Zimbabwe were included. TAF PK results (table 1) from TAF combined with DTG, DRV/r or LPV/r were comparable to adult reference values with AUClast at GM (CV%) 284.5 (79), 232.0 (61), and 210.2 (98) ng*h/mL, respectively. TAF combined with ATV/r resulted in increased TAF concentrations with AUClast 511.4 (68) ng*h/mL. For each combination, TFV GM $AUC_{tau}$ and $C_{max}$ remained below reference values in adults taking 25mg TAF with a boosted regimen. Safety continues to be monitored by an independent data monitoring committee.

**Conclusion:** TAF combined with one of 3 PIs or DTG provides concentrations in children demonstrated to be well tolerated and effective in adults. This provides evidence for TAF dosing in practical regimens to be available in low and middle income countries. Further PK data collection is ongoing including measurement of intracellular TFV levels in dried blood spots and population pharmacokinetic modelling. Safety is being monitored in all children.

Table 1: Pharmacokinetic parameters of TAF/TFV dosed in weight bands combined with four anchor drugs

| | TAF + DTG | TAF + ATV/r | TAF + DRV/r | TAF + LPV/r | Reference adults | |
|---|---|---|---|---|---|---|
| TAF dose and boosting | <25kg: 15mg ≥25kg: 25mg unboosted | <25kg: 15mg ≥25kg: 25mg boosted | <25kg: 15mg ≥25kg: 25mg boosted | <25kg: 15mg ≥25kg: 25mg boosted | 25mg TAF unboosted/ 10mg TAF boosted[ab] | 25mg TAF DRV/cobi boosted[a] |
| N participants | 18 | 32 | 34 | 20 | 539 | 11 |
| Age in years on PK day median (range) | 10.9 (5.5-14.2) | 10 (4.8-15) | 10.9 (3.8-14.7) | 11.2 (4.3-14.6) | - | - |
| Weight in kg on PK day median (range) | 25.9 (15.9-53) | 25.8 (14.5-50) | 24 (14.5-47) | 25.5 (14.2-48.5) | - | - |
| Sex male, n (%) | 8 (44%) | 15 (47%) | 16 (47%) | 9 (45%) | - | - |
| TAF | | | | | | |
| $AUC_{last}$ (ng*h/mL) | 284.5 (79) | 511.4 (68) | 232.0 (61) | 210.2 (98) | 206.4 (72) | 222 (na) |
| $C_{max}$ (ng/mL) | 145.1 (91) | 300.9 (83) | 155.0 (104) | 155.5 (107) | 162.2 (51) | 181 (na) |
| CL (L/H) | 55 (95) | 31 (43) | 82 (75) | 73 (86) | 65.0 (53) | - |
| Vd (L) | 79 (165) | 38 (71) | 98 (96) | 102 (78) | - | - |
| TFV | | | | | | |
| $AUC_{tau}$ (ng*h/mL) | 323.9 (29) | 849.1 (37) | 744.6 (26) | 864.4 (46) | 292.6 (27) | 937 (na) |
| $C_{max}$ (ng/mL) | 19.6 (26) | 53.8 (41) | 44.6 (26) | 50.3 (43) | 15.2 (26) | 56 (na) |

Pharmacokinetic data is presented as geometric mean (GM) with coefficient of variation (CV%). na: not available, TAF: tenofovir alafenamide fumarate, DTG: dolutegravir, ATV/r: atazanavir/ritonavir, DRV/r: darunavir/ritonavir, LPV/r: lopinavir/ritonavir, PK: pharmacokinetic, GM: geometric mean, AUC: area under the concentration-time curve from 0 to 24h ($AUC_{tau}$) or from 0 to the last sample with a measurable concentration ($AUC_{last}$), $C_{max}$: highest concentration of pharmacokinetic curve. a: FDA Descovy CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW b: Gaur, A. et al. Lancet HIV 2016; 3: e561–68

## 735 PHARMACOKINETICS OF ABACAVIR IN AFRICAN CHILDREN <14 KG DOSED PER WHO WEIGHT-BANDS

New Investigator Scholar

**Suthunya Chupradit**[1], Dalton C. Wamalwa[2], Elizabeth Maleche-Obimbo[2], Adeodata R. Kekitiinwa[3], Juliet Mwanga-Amumpaire[4], Elizabeth A. Bukusi[5], Winstone M. Nyandiko[6], Joseph K. Mbuthia[7], Alistair Swanson[8], Tim R. Cressey[1], Baralee Punyawudho[1], Victor Musiime[9]

*[1]Chiang Mai University, Chiang Mai, Thailand, [2]University of Nairobi, Nairobi, Kenya, [3]Baylor College of Medicine Children's Foundation, Kampala, Uganda, [4]Epicentre, Mbarara, Uganda, [5]Kenya Medical Research Institute, Kisumu, Kenya, [6]The Academic Model Providing Access to Healthcare and Moi University, Moi Teaching and Referral Hospital, Eldoret, Kenya, [7]Gertrude's Children's Hospital, Nairobi, Kenya, [8]Drug for Neglected Diseases Initiative, Geneva, Switzerland, [9]Joint Clinical Research Centre, Kampala, Uganda*

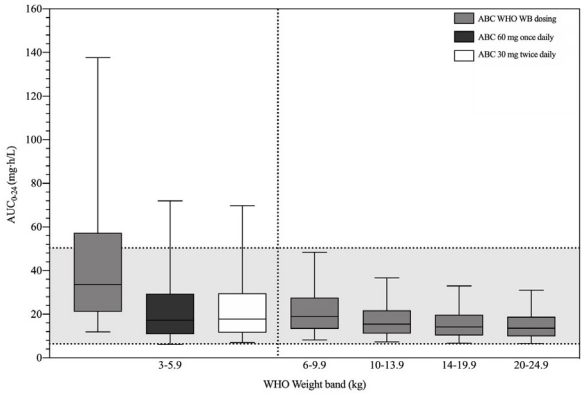
**Background:** There are limited abacavir (ABC) pharmacokinetic (PK) data in African children living with HIV (CLHIV) <14 kg receiving pediatric fixed-dose combinations (FDC) dosed by WHO weight-bands (WB). WB dosing with FDC tablets leads to higher than FDA-approved mg/kg daily doses of ABC in the lower WBs. We developed an ABC population PK model using clinical data from Kenyan and Ugandan CLHIV to assess ABC exposures across WBs.

**Methods:** Children enrolled in the LIVING study in Kenya and Uganda [NCT02346487] who received ABC/3TC (60/30 mg) dispersible tablets and LPV/r (40/10 mg) pellets BID according to WHO WB were included. Sparse PK samples were collected after 1 month, and every 6 months for up to 30 months. PK parameters were estimated using a population approach. Using the final model, simulations were performed using a standardized in silico paediatric population with demographics representative of African CLHIV to predict ABC exposure across WBs. Target daily ABC exposures (AUC0-24) were those reported in older children (6.4 to 50.4 mg.h/L).

**Results:** A total of 2,254 ABC plasma samples were available from 387 children (49.6% female). At baseline, mean (range) age was 2.91 (0.3-9.7) years, body weight was 11.95 (4.4-23) kg, 16% were moderately and 10% severely underweight. ABC PK was described by a 1-compartment model. Body weight influenced clearance (CL/F) and volume of distribution (V/F) and was allometrically scaled. Maturation of ABC CL/F was described using a sigmoid model dependent on post-natal age (50% adult CL/F achieved by 0.48 yrs old). ABC CL/F, V/F and Ka were 21.4 L/h, 7.2 L (standardized to a 12.9 kg child) and 0.37 h-1, respectively. ABC exposures were within target for children 6.0-24.9 kg but higher exposures were seen for children 3-5.9 kg (Figure 1). Reducing the ABC dose to 30 mg BID or 60 mg OD for children 3-5.9 kg achieved a higher proportion within target.

**Conclusion:** Twice daily WHO WB dosing of FDC tablets containing 60 mg ABC provide adequate exposure in children ≥6 kg; however, higher exposures are expected for children 3.0-5.9 kg. While no safety concerns have been reported with the current dosing, lower ABC doses (30 mg BID or 60 mg OD) in WB 1 would be optimal to achieve comparable exposures.

**Figure 1:** Daily ABC exposure ($AUC_{0-24}$) by WHO weight-band BID dosing (grey). Alternative ABC doses 60 mg OD (black) and 30 mg BID (white) are also shown for the lowest WB. Target $AUC_{0-24}$ (6.4 to 50.4 mg.h/L) (shaded area).




## 736 PHARMACOKINETICS/SAFETY OF DTG, ABC/3TC DISPERSIBLE TABLETS IN THAI CHILDREN <20 KG

**Athiporn Premgamone**[1], Suvaporn Anugulruengkitt[1], Noppadol Wacharachaisurapol[1], Chayapa Phasomsap[1], Monta Tawan[1], Thidarat Jupimai[1], Chutima Saisaengjan[1], Yardpiroon Tawon[2], Tim R. Cressey[2], Thanyawee Puthanakit[1]

*[1]Chulalongkorn University, Bangkok, Thailand, [2]Chiang Mai University, Chiang Mai, Thailand*

**Background:** Dolutegravir (DTG) and abacavir/lamivudine (ABC/3TC) generic dispersible tablets (DT) are recommended for use in young children with HIV. Pharmacokinetic (PK) data of these generic scored dispersible tablets administered once daily together are limited. This study aimed to describe PK data of DTG-DT with ABC/3TC-DT in young children weighing 6 to <20 kg in Thailand.

**Methods:** Children living with HIV weighing between 6 to <20 kg aged from 3 months to 7 years were eligible. DTG-DT (10 mg, Mylan Inc, VIARTISTM) and ABC/3TC-DT (120/60 mg, Mylan, VIARTISTM)) were dosed using the following weight bands (WBs): 6-9.9 kg, 20/180/90 mg; 10-13.9 kg, 20/240/120 mg; and 14-<20 kg, 25/300/150 mg. Doses prescribed were in accordance with WHO recommendations, except for those in the 6-9.9 kg WB where DTG 20 mg rather than 15 mg was used. Pharmacokinetic studies were performed at steady-state (7-14 days after regimen initiation). Blood samples were collected at pre-dose and at 1, 2, 3, 4, 6, and 24 h post-dose. Results were compared with AUC0-24, CAUC24, $C_{max}$ reported from the ODYSSEY trial (for DTG) and the ARROW study (for ABC/3TC). PK analyses were performed using Phoenix WinNonlin version 8.3 (Clinical trials registration: TCTR20201025001)

**Results:** From 2 August 2021 to 3 October 2021, 18 children were enrolled with median age of 4.5 years (2.8-5.8) and 11 (61%) were male. Median (IQR) weight within each weight band were 9.4 kg (8.3-9.7), 12.8 kg (11.4-13.5), and 15.6 kg (15-19.9). Eleven were HIV RNA virologically suppressed and 7 viremic. DTG, ABC, and 3TC PK parameters are shown in Table 1. DTG AUC0-24, $C_{max}$, and C 24values were generally higher than those reported in the ODYSSEY trial across all weight bands. DTG C 24 in WB 6-9.9 24 with 20 mg was closer to that observed in older children but highly variable. ABC/3TC for the 10-19.9 kg WB exposures trended

higher compared with the ARROW study. There is no serious adverse event among all participants.

**Conclusion:** Generic DTG and ABC/3TC generic scored dispersible tablets provided adequate drug exposures in Thai children weighing 6 to <20 kg. DTG 20 mg in the lowest weight band produced higher drug exposure and C24. These initial data suggested that a DTG and ABC/3TC regimen with a slightly modified WHO weight band doses will be efficacious and safe for Thai children weighing <20 kg.

Table 1. Pharmacokinetic parameters of the generic scored dispersible tablets of dolutegravir, abacavir, lamivudine

| | | | | | |
|---|---|---|---|---|---|
| **DTG** | | **Weight band [no. of participants] and dose** | | | **Historical references** |
| | **PK parameters** | **6-9.9 kg [n=3] 20 mg** | **10-13.9 kg [n=4] 20 mg** | **14-19.9 kg [n=11] 25 mg** | **ODYSSEY 14-19.9 kg 25 mg** |
| | $AUC_{0-24}$, mg·h/L | 93.6 (41.2-212.7) | 74.3 (56.1-98.3) | 90.2 (77.1-105.5) | 69.5 (30) |
| | $C_{max}$, mg/L | 9.0 (5.7-14.1) | 8.4 (5.3-13.2) | 7.9 (7.2-8.8) | 7.1 (21) |
| | $C_{24}$, mg/L | 1.1 (0.3-4.4) | 0.8 (0.5-1.2) | 1.3 (1.0-1.7) | 0.8 (67) |
| **ABC** | | **Weight band [no. of participants] and dose, mg/kg** | | | |
| | **PK parameters** | **6-9.9 kg [n=2] 180 mg** 21 (16.3-27.7) | **10-13.9 kg [n=4] 240 mg** 20 (17.8-22.4) | **14-19.9 kg [n=11] 300 mg** 18.4 (17.3-19.6) | **ARROW 3-6 y** 18.8 (17.7-20.0) |
| | $AUC_{0-24}$, mg·h/L | 12.2 (0.2-929.9) | 19.4 (12.5-30.0) | 21.0 (17.4-25.5) | 15.0 (12.3-18.3) |
| | $C_{max}$, mg/L | 5.9 (0.2-233.7) | 8.6 (5.9-12.6) | 8.8 (7.8-10.0) | 6.8 (5.7-8.1) |
| **3TC** | | **Weight band [no. of participants] and dose, mg/kg** | | | |
| | **PK parameters** | **6-9.9 kg[n=2] 90 mg** 10.6 (8.1-13.8) | **10-13.9 kg [n=4] 120 mg** 10.0 (8.9-11.2) | **14-19.9 kg [n=11] 150 mg** 9.2 (8.6-9.8) | **ARROW 3-6 y** 9.4 (8.8-10.0) |
| | $AUC_{0-24}$, mg·h/L | 11.5 (0.1-1314.0) | 20.3 (13.4-30.9) | 20.8 (18.1-24.0) | 12.3 (10.3-14.7) |
| | $C_{max}$, mg/L | 3.1 (0.1-71.9) | 5.3 (4.6-6.2) | 4.7 (4.3-5.3) | 3.0 (2.5-3.6) |

Data are presented as geometric means (GM; 95% confidence interval) except for ODYSSEY, which is presented as geometric means (GM; %CV); and median age, which is presented as median (IQR).

PK – pharmacokinetic, CV – coefficient variation, IQR – interquartile range, DTG – dolutegravir, ABC – abacavir, 3TC – lamivudine

## 737 IMPAACT 2019: PK & SAFETY OF DISPERSIBLE ABC/DTG/3TC IN CHILDREN WITH HIV 6 TO <14 KG

**Kristina M. Brooks**[1], Jennifer Kiser[1], Yasha Rani[2], Gaerolwe Masheto[3], Faeezah Patel[4], Iris Mustich[5], Barbara Heckman[6], Mark Lojacono[6], Dwight E. Yin[7], Sai Majji[8], Hardik Chandasana[9], Helena Rabie[10], Patricia Flynn[11]

*[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Frontier Science & Technology Research Foundation, Brookline, MA, USA, [3]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [4]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [5]FHI 360, Durham, NC, USA, [6]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [7]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, [8]National Institute of Child Health and Human Development, Bethesda, MD, USA, [9]GlaxoSmithKline, Collegeville, PA, USA, [10]Stellenbosch University, Stellenbosch, South Africa, [11]St Jude Children's Research Hospital, Memphis, TN, USA*

**Background:** IMPAACT 2019 is a Phase I/II, multi-site, open-label dose confirmation study examining the pharmacokinetics (PK), safety, and tolerability of once-daily abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) in immediate-release (IR) and dispersible tablet (DT) form. We previously confirmed dosing of IR and DT ABC/DTG/3TC in children ≥14 to <40 kg. We now report intensive PK and week 4 safety results for DT ABC/DTG/3TC in children weighing 6 to <14 kg.

**Methods:** Children <12 years of age were enrolled across five weight bands (WB) in Botswana, South Africa, Thailand, and the United States. Data are presented for: WB1 6-<10kg (3 DT in 15 mL water: ABC 180 mg/DTG 15 mg/3TC 90 mg) and WB2 10-<14kg (4 DT in 20 mL water: ABC 240 mg/DTG 20 mg/3TC 120 mg). Children could be treatment-naïve or -experienced with an HIV VL <200 copies/mL and on a non-NNRTI containing regimen for ≥6 months at entry. Intensive PKs were performed 5-10 days post-entry with dosing confirmed for ≥4 days prior. Samples were collected at time 0 (pre-dose), 1, 2, 3, 4, 6, 8, and 24 hours post-dose following an overnight fast (low-fat light snack permitted ≥2 hours prior to observed dose). Dose confirmation was based on meeting PK and safety criteria. PK targets for each WB were geometric mean (GM) point estimates within the target ranges in the table, and were based on historical PK data in adults and children with HIV. Acceptable safety criteria were: no deaths/life-threatening adverse events (AEs) related to study drug, and grade 3+ AEs or permanent discontinuation related to study drug in <2 participants.

**Results:** 14 children underwent intensive PK (7 per WB). Demographic and PK results are summarized in the table. No grade 3+ AEs related to study drug occurred and no AEs led to study drug discontinuation. One participant in WB1 experienced the following events: grade 3 fever (unrelated), a grade 2 eGFR decrease and grade 1 serum creatinine increase from baseline (both related to DTG; absolute values within normal range). Another participant in WB1 experienced a grade 1 ALT elevation (related to ABC, DTG, and 3TC).

**Conclusion:** PK and safety criteria were met for DT ABC/DTG/3TC in children weighing 6 to <14kg, which provides reassurance for dosing of DT ABC/DTG/3TC in these WBs. Long-term safety and tolerability data through 48 weeks for all WBs will be forthcoming.

**Table. Participant Demographics & PK Results**

| Characteristic | Weight Band 1 (n=7) | Weight Band 2 (n=7) |
|---|---|---|
| **Demographics** | | |
| Age (year), median (range) | 1.6 (1.1-2.0) | 3.6 (2.1-4.0) |
| Weight on Day of Intensive PK (kg), median (range) | 9.5 (8.3-9.8) | 13.1 (11.2-14.2) |
| Female sex at birth, n(%) | 5 (71%) | 4 (57%) |
| Treatment-Experienced, n(%) | 5 (71%) | 7 (100%) |
| **PK Results (geometric mean (geometric CV%))** | | |
| DTG $AUC_{0-24h}$ (µg·h/mL) [target: 35.1-134 µg·h/mL] | 75.9 (33.7%) | 91.0 (36.5%) |
| DTG $C_{24h}$ (µg/mL) [target: 0.67-2.97 µg/mL] | 0.91 (67.6%) | 1.22 (77.5%) |
| ABC $AUC_{0-24h}$ (µg·h/mL) [target: 6.3-50.4 µg·h/mL] | 17.7 (33.9%) | 19.8 (50.6%) |
| 3TC $AUC_{0-24h}$ (µg·h/mL) [target: 6.3-26.5 µg·h/mL] | 10.7 (46.0%) | 14.2 (23.9%) |

$AUC_{0-24h}$: area under the concentration vs. time curve from time 0 to 24 hours post-dose; $C_{24h}$: concentration at 24 hours post-dose.

## 738 SAFETY AND PK OF LONG-ACTING CABOTEGRAVIR AND RILPIVIRINE IN ADOLESCENTS

**Carolyn Bolton Moore**[1], Edmund Capparelli[2], Katherine Calabrese[3], Brookie M. Best[2], Shawn Ward[4], Cindy McCoig[5], Herta Crauwels[6], Allison Agwu[7], Pearl Samson[4], Barbara Heckman[4], Susan L. Ford[8], Adeola Adeyeye[9], Andres Camacho-Gonzalez[10], Jack Moye[11], Aditya H. Gaur[12]

*[1]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [2]University of California San Diego, La Jolla, CA, USA, [3]FHI 360, Durham, NC, USA, [4]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [5]ViiV Healthcare, Collegeville, PA, USA, [6]Janssen Research & Development, LLC, Pennington, NJ, USA, [7]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [8]GlaxoSmithKline, Research Triangle Park, NC, USA, [9]National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, [10]Emory University, Atlanta, GA, USA, [11]National Institute of Child Health and Human Development, Bethesda, MD, USA, [12]St Jude Children's Research Hospital, Memphis, TN, USA*

**Background:** Long-acting cabotegravir (CAB-LA) plus long-acting rilpivirine (RPV-LA) are now approved for maintenance of viral suppression in adults with HIV-1 infection. IMPAACT 2017 (MOCHA) is a phase I/II non-comparative, open label study to confirm the dose and evaluate safety, tolerability, acceptability, and pharmacokinetics (PK) of oral CAB, CAB-LA, and RPV-LA in adolescents, ≥12 to <18 years, living with HIV-1. Here we present data-to-date from Cohort 1, Q4W, of the study.

**Methods:** Virologically suppressed (viral load <50 copies/mL) adolescents living with HIV-1 and on stable combination antiretroviral therapy (cART) were enrolled into Cohort 1C (CAB) or Cohort 1R (RPV) based on background cART. After 4 weeks of oral lead-in with either CAB (30mg once daily) or RPV (25mg once daily), participants received CAB-LA (600mg/3mL at Week 4 and 400mg/2mL at Weeks 8 and 12) or RPV-LA (900mg/3mL at Week 4 and 600mg/2mL at Weeks 8 and 12) by gluteal intramuscular (IM) injection. Background cART was retained throughout Cohort 1. PK samples were drawn at Week 2 (to assess oral dosing) and Weeks 4, 5, 6, 8, 12, 13, 14 and 16 (to assess LA dosing).

**Results:** At the time of this analysis, 23 participants enrolled with two premature treatment discontinuations of study drug, both in Cohort 1R; one due to hypersensitivity (after 1st oral dose) and one due to pain with needle insertion prior to receiving first IM injection. Cohort 1C included 6 males and 2 females with median (range) age 14.5 (12-17) years and weight 57 (43-73.5) kg; Cohort 1R included 7 males and 8 females with median (range) age 17.0 (12-17) years and weight 63 (44.1-98.5) kg. All injection site reactions were grade 1 or 2 and none led to discontinuation. Through Week 16 there was one Grade 3 drug-related adverse event in each cohort (insomnia, 1C) and (hypersensitivity, 1R, leading to study withdrawal). The median PK parameters were within the desired study targets, based on achieving comparable exposure in adolescents and adults with median (range) presented. Cohort 1C Week 2 Oral CAB AUC0-τ: 160 (94.3-325) mcg*h/mL (target median 46-277), Week 16 IM CAB trough: 3.11 (1.22-6.19) mcg/mL (target median 0.71-6.7). Cohort 1R Week 16 IM RPV trough: 52.9 (31.9-148) ng/mL (target for median 25-100).

**Conclusion:** IM administration of CAB-LA or RPV-LA in adolescents achieved target exposure concentrations consistent with predictions and were comparable to adults receiving monthly IM dose regimens. No new or unanticipated safety concerns were identified.

## 739 ADOLESCENT AND PARENT EXPERIENCES WITH LONG-ACTING INJECTABLES IN THE MOCHA STUDY

**Elizabeth D. Lowenthal**[1], Jennifer Chapman[2], Katherine Calabrese[3], Ryan Milligan[4], Allison Agwu[5], Andres Camacho-Gonzalez[6], Christiana Smith-Anderson[7], Jared Kneebone[8], Cindy McCoig[9], Conn M. Harrington[10], Rodica Van Solingen-Ristea[11], Adeola Adeyeye[12], Jack Moye[13], Carolyn Bolton Moore[14], Aditya H. Gaur[15]

*[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Children's Hospital of Philadelphia, Philadelphia, PA, USA, [3]FHI 360, Durham, NC, USA, [4]Frontier Science and Technology Research Foundation, Inc, Brookline, MA, USA, [5]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [6]Emory University, Atlanta, GA, USA, [7]University of Colorado, Aurora, CO, USA, [8]Frontier Science and Technology Research Foundation, Inc, Buffalo, NY, USA, [9]ViiV Healthcare, Madrid, Spain, [10]ViiV Healthcare, Research Triangle Park, NC, USA, [11]Janssen, Beerse, Belgium, [12]National Institutes of Health, Rockville, MD, USA, [13]National Institutes of Health, Bethesda, MD, USA, [14]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [15]St Jude Children's Research Hospital, Memphis, TN, USA*

**Background:** The ongoing More Options for Children and Adolescents Study (MOCHA; Clinicaltrials.gov NCT03497676) is the first to examine use of long-acting injectable (LA) antiretrovirals (ARV) (cabotegravir [CAB-LA] and rilpivirine [RPV-LA]) in adolescents, 12 to <18 years old, living with HIV-1. While LA may improve adherence and viral suppression, little is known about the acceptability of this treatment approach for adolescents.

**Methods:** To assess LA acceptability issues of importance to adolescents, participants completed questionnaires about reasons for choosing the LA regimen, perceptions of injections, and health-related quality of life (PedsQLTM) at study entry and after receipt of 3 injectable doses (CAB-LA or RPV-LA). In-depth interviews (IDIs) were conducted by phone sequentially with adolescent participants and separately with parents/caregivers ("parents") of participants who were English-speaking and agreed to IDIs. Interview transcripts were coded and analyzed thematically using the consolidated framework for advancing implementation research.

**Results:** To date, as part of Cohort 1 of MOCHA, 21 virologically suppressed adolescents received 3 IM injections of CAB-LA or RPV-LA 4 weeks apart (in addition to their stable oral combination ARVs) for an initial pharmacokinetic evaluation and completed the noted questionnaires. For 16 adolescents (76.2%), the primary reason for enrolling was the desire to avoid having to take daily pills or finding it difficult to take daily pills. Of 21 adolescents who received 3 study injections, 90.5% (19/21) reported wanting to receive injectable medicines even when not in the study. PedsQLTM scores indicated overall good quality of life at both study entry and following the 3 injections. 11 adolescents and 11 parents underwent IDIs. In the IDIs, themes related to not having to remember to take pills/avoiding the stress of monitoring adolescents' daily medication-taking and not having to worry about hiding pills from peers dominated discussions of the relative advantage of LA versus pills. Concerns regarding long-term use of LA ARVs included questions about ability to maintain a routine injection schedule when busy with school, extracurricular activities, and work, particularly for those planning to move to college.

**Conclusion:** Feedback from adolescents receiving CAB-LA or RPV-LA to date was overall favorable. Issues and concerns identified will help inform future studies and implementation planning when LAs become commercially available for this age group.

## 740 COVID-19 IN CHILDREN: WORSENING OUTCOMES DURING DELTA VARIANT WAVE

Late Breaking

**Christiana Smith-Anderson**[1], Lori Silveira[2], Monika Jelic[2], Sean Lang[2], Shane Curran-Hays[2], Ye Ji Choi[2], JoEllen Fresia[2], Brian Carter[2], Shea Boyer[2], Lisa Abuogi[2]

*[1]University of Colorado, Aurora, CO, USA, [2]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** Pediatric cases of COVID-19 surged in the summer/fall of 2021 coinciding with the SARS-CoV-2 Delta variant. It is unclear whether the Delta variant caused more severe illness among pediatric patients. We leveraged the Children and COVID-19 in Colorado database to determine whether differences exist in demographics, underlying comorbidities, and outcomes among children requiring hospital admission due to the SARS-CoV-2 Delta variant vs. wild type virus.

**Methods:** We performed a retrospective review of children <21 years with symptomatic COVID-19 and detectable SARS-CoV-2 NAAT hospitalized at Children's Hospital Colorado during pre-Delta (Mar-Nov 2020) and Delta (Jun-Sep 2021) periods. We compared variables using Fisher's exact or Pearson's chi square tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

**Results:** There were 119 children hospitalized with symptomatic COVID-19 during the pre-Delta and 137 in the Delta period. There was a slight male predominance in both periods. Children hospitalized during the Delta period were younger, with median (interquartile range) age of 5.9 (1.0-14.5) vs. 12.2 (1.5-16.9) years, p=0.02; and were less likely to identify as Hispanic and Spanish-speaking, compared to the pre-Delta period (Table). There was a trend toward decreasing proportions of hospitalized children with underlying comorbidities in the Delta vs. pre-Delta period (59.1% vs. 69.8%; p=0.07). The most prevalent types of comorbidities were similar between periods; but the proportion of hospitalized immunocompromised patients was lower in the Delta vs. pre-Delta period (p=0.005). Half of all children were overweight/obese in both periods. Similar proportions of hospitalized children required respiratory support in both periods, but more children required intensive care in the Delta vs. pre-Delta periods (36.5% vs. 23.5%, p=0.03).

**Conclusion:** Children hospitalized with the Delta variant of COVID-19 were younger, less likely to be Hispanic, and had fewer comorbidities than children hospitalized with wild type SARS-CoV-2. Children hospitalized with the Delta variant were more likely to require ICU admission compared to children hospitalized with wild type SARS-CoV-2, which may indicate increased severity of the Delta variant in the pediatric population. Close monitoring of pediatric outcomes is needed as new SARS-CoV-2 variants emerge.

| | | Pre-Delta period (Mar-Nov 2020) N=119 | Delta period (Jun-Sep 2021) N=137 | p-value |
|---|---|---|---|---|
| DEMOGRAPHICS | Male | 65 (54.6%) | 72 (62.6%) | 0.80 |
| | Age (years), median (IQR) | 12.2 (1.5-16.9) | 5.9 (1.0-14.5) | **0.02** |
| | Hispanic | 70 (62.0%) | 50 (41.7%) | **0.04** |
| | Non-Hispanic white | 24 (21.2%) | 47 (39.2%) | |
| | Non-Hispanic other | 19 (16.8%) | 23 (19.2%) | |
| | English-speaking | 81 (68.1%) | 124 (90.5%) | **<0.0001** |
| | Spanish-speaking | 34 (28.6%) | 10 (7.3%) | |
| | Other language | 4 (3.3%) | 3 (2.2%) | |
| COMORBIDITIES | Any comorbidity | 83 (69.8%) | 81 (59.1%) | 0.07 |
| | Immunocompromised | 18 (15.1%) | 6 (4.4%) | **0.005** |
| | Overweight | 40 (50.0%) | 42 (49.4%) | 1.0 |
| | Obese *subset of overweight | 30 (37.5%) | 30 (35.3%) | 0.87 |
| OUTCOMES | Intensive care | 28 (23.5%) | 50 (36.5%) | **0.03** |
| | Any respiratory support | 60 (50.4%) | 80 (58.4%) | 0.21 |
| | Low flow oxygen | 35 (58.3%) | 38 (47.5%) | 0.31 |
| | High flow oxygen | 5 (8.3%) | 11 (13.7%) | |
| | Non-invasive positive pressure | 9 (15.0%) | 21 (26.3%) | |
| | Intubation/ventilation | 9 (15.0%) | 9 (11.2%) | |
| | ECMO | 2 (3.3%) | 1 (1.3%) | |

## 741 LONGITUDINAL STUDY OF ANTI-SPIKE ANTIBODIES IN CHILDREN AFTER SARS-CoV-2 INFECTION

New Investigator Scholar

**Federica Frasca**[1], Leonardo Sorrentino[1], Giuseppe Oliveto[1], Mirko Scordio[1], Matteo Fracella[1], Agnese Viscido[1], Fabio Midulla[1], Raffaella Nenna[1], Alessandra Febbo[1], Luigi Matera[1], Guido Antonelli[1], Carolina Scagnolari[1], Alessandra Pierangeli[1]

*[1]Sapienza University of Rome, Rome, Italy*

**Background:** Children generally develop asymptomatic or mild COVID-19 disease, despite the exact mechanisms that protect them from severity are yet to be defined. Since humoral response to SARS-CoV-2 infection in children is still poorly investigated, we aimed to analyze circulating levels of anti-Spike IgA and IgG in pediatric population up to 8 months after SARS-CoV-2 infection, to delineate whether COVID-19 outcomes could impact on antibody (Ab) levels.

**Methods:** A total of 115 COVID-19 young patients (mean age: 11.5 years, range 1-19 years) were enrolled between October 2020 and March 2021. All cases were confirmed SARS-CoV-2 infection by use of a diagnostic molecular assay on nasopharyngeal swabs. Circulating anti-SARS-CoV-2 IgG and IgA were measured using ELISA assays at one-month (T1), two-month (T2) and eight-month (T3) follow-up blood samples of young partecipants.

**Results:** Longitudinal observation of COVID-19 children showed a decreased circulating level of IgA at T2 and T3 respectively compared to T1 (p<0.001). Persistent levels of anti-Spike IgG were observed at least two-month post infection but they significantly decreased at T3 (p<0.001). Stratifying children in two age-classes (1-9 and 10-19 years old) we found significantly higher levels of IgA in younger children at T1, T2 and T3 than in children older than 10 years old (p=0.012; p=0.041; p=0.036, respectively). Differently, younger children had a significantly higher level of IgG at T2 (p=0.029) and at T3 (p=0.049), but not at T1. Stratifying children based on the presence or absence of SARS-CoV-2 correlated symptoms or on the basis of underlying diseases, we did not observe differences in blood levels of IgA and IgG in all time points analyzed.

**Conclusion:** Our longitudinal data indicated that younger children are characterized by an elevated peak of early IgA and are also defined by a robust induction of IgG, with respect to the older. These results contrast with what is common in SARS-CoV-2 infection in adults that elicit higher levels of polyfunctional Abs in severe disease. If confirmed in larger groups, these data would suggest that pediatric patients that usually have an efficient control of SARS-CoV-2 infections without inflammation would also elicit a humoral immune response protective from reinfections.

## 742 HUMORAL AND CELLULAR RESPONSE TO mRNA SARS-CoV-2 VACCINATION IN HIV-INFECTED CHILDREN

**Jose Tomas Ramos Amador**[1], Arantxa Berzosa Sanchez[2], Marta Illan[2], Alba Ruedas[2], Kauzar M. Mohamed Mohamed[1], Luis Prieto[3], Sara Guillén[4], Ignacio Callejas[5], Ana Belén Jiménez[6], Santiago Jiménez de Ory[7], María Luisa Navarro[7], Silvia Sanchez-Ramon[2]

*[1]Clínico San Carlos Hospital, Madrid, Spain, [2]Hospital Universitario Clínico San Carlos, Madrid, Spain, [3]Hospital Universitario 12 de Octubre, Madrid, Spain, [4]Hospital de Getafe, Madrid, Spain, [5]Hospital Universitario de Getafe, Madrid, Spain, [6]Fundacion Jimenez Diaz, Madrid, Spain, [7]Hospital General Universitario Gregorio Marañón, Madrid, Spain*

**Background:** There are still scant data on the immunogenicity of SARS-CoV-2 mRNA vaccination in PWH, and no experience in HIV-infected adolescents has been reported.

**Methods:** A prospective ongoing observational study is being conducted in HIV-infected adolescents after the introduction of mRNA vaccination in Spain starting in August, 2021. Blood samples were drawn 3-8 weeks after the second dose of BNT162b2(Pfizer/BioNTech) and CoV-2 mRNA-1273(Moderna) vaccines in 15 HIV-infected adolescents and were compared to 19 matched healthy subjets. Humoral response was assesed by detection of SARS-CoV-2 antibodies by chemiluminescent microparticle immunoassay (CMIA,Alinity® Quant assay-Abbott) to detect IgG against S1 region of the spike protein of SARS-CoV-2 (≥50U/mL considered reactive). T-Cell response to SARS-CoV-2 was measured by an interferon-gamma released assay (IGRA,Euroimmun) of S1 peptide-stimulated T-cells in whole blood (≥200mIU/ml considered reactive).

**Results:** Fifteen HIV-infected adolescents (11female) were included, after administration of mRNA vaccination (13 Pfizer, 2 Moderna). All but 1 were perinatally infected, 10 Caucasian, 3 Latino and 2 from Sub-saharan Africa. Median age was 16.2 years (IQR12.7-19.2) and 14.3 years (IQR12.7-19.2), in patients and controls(p>0.05). Four patients were on CDC-Class C or 3. Median baseline CD4+ count was 703 cells/ul (IQR 596-1098). All were on integrase inhibitors-based ART (13had undetectable viral load). The nadir CD4 was 446 cells/ul (IQR 596-1098). Median interval days since last vaccine dose in HIV-infected adolescents and controls were 33 days(IQR29-49) and 33.5 days(IQR27-45), respectively(p>0.05). All patients and controls had reactive humoral and celular responses. HIV-infected subjects had lower anti-Spike antibodies titers (median:11320U/mL, IQR6074-21518) than controls (median: 30342 AU/mL, IQR9222-38013) (p=0.001). No significant differences were observed in cellular immune responses in HIV-infected adolescents (median 1759mIU/ml, IQR:1613-1856) vs controls (median 1853mIU/ml, IQR1782-1873) (p=0.12). No correlation was observed between quantitative humoral and cellular responses

**Conclusion:** HIV-infected adolescents with good immuno-virologic status show appropriate specific antibody levels and cellular immune responses against SARS-CoV-2 shortly after mRNA vaccination. Although they appear to mount a similar quantitative celular inmune response, the elicited antispike antibody levels was lower than that in healthy controls.

## 743 BAMLANIVIMAB PLUS ETESEVIMAB FOR THE TREATMENT OF COVID-19 IN PEDIATRIC PATIENTS

**Himanshu P. Upadhyaya**[1], Jenny Chien[1], Martin Bohm[1], Lisa Macpherson[1], Dipak R. Patel[1], Matthew M. Hufford[1], Mark Williams[1]

*[1]Eli Lilly & Company, Indianapolis, IN, USA*

**Background:** There are no authorized or approved treatments in the US for COVID-19 in patients <12 years of age. SARS-CoV-2 neutralizing monoclonal antibodies bamlanivimab and etesevimab together (BAM+ETE) reduce COVID-19 related hospitalization and all-cause mortality in patients ≥12 years of age with mild to moderate COVID-19. Herein, we present the pharmacokinetic (PK), safety, and efficacy results from an open-label Phase III clinical trial addendum (BLAZE-1, NCT04427501) investigating weight-based dosing of BAM+ETE in pediatric patients at increased risk for severe COVID-19.

**Methods:** A total of 91 pediatric patients (<18 years of age) were evaluated for PK. Pediatric patients weighing ≥40kg received 700mg BAM+1400mg ETE. Pediatric patients weighing less than 40kg received weight-based dosing to match the exposures observed in adults and adolescents (12 to <18 years of age) who received the authorized dose of 700mg BAM+1400mg ETE. Twenty additional adolescent patients (12 to <18 years of age) received BAM+ETE in controlled BLAZE-1 cohorts and were included in safety and efficacy analyses. All ambulatory patients had mild to moderate COVID-19 upon enrollment, at least one risk factor for severe COVID-19, and received treatment within 3 days of a positive SARS-CoV-2 test. The primary objective was to characterize the pharmacokinetics of weight-based dosing of BAM+ETE in pediatric patients.

**Results:** Of the 111 pediatric patients who received BAM+ETE, the median age was 12 and age distribution was 12 to <18 (n=60), 6 to <12 (n=36), 2 to <6 (n=10), and 0 to <2 (n=5). Overall, 47.7% were female, 19.1% were Hispanic/Latino, and 62.4% were Black/African American. In patients receiving weight-based dosing, the AUC for both BAM and ETE in pediatric patients was similar (within 90% interval) to adults (Figure). For all pediatric patients, there were no reports of hospitalizations, serious adverse events, or deaths. At Day 7, pediatric patients had a change in viral load from baseline of -4.10 (normalized baseline viral load of 6.41) as compared to -3.65 (normalized baseline viral load of 6.75) in adult patients. The median time to complete symptom resolution was 5 days for all pediatric patients.

**Conclusion:** The weight-based doses administered to pediatric patients provided similar drug exposures when compared to adult patients who received the authorized dose of 700 mg BAM+1400mg ETE. Treatment in pediatric patients was well-tolerated and resulted in favorable viral load reduction and symptom resolution.

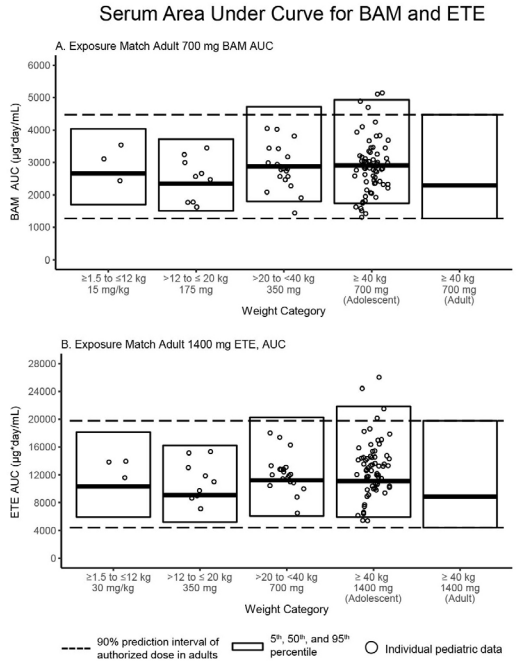



FIGURE: Individual estimated AUCs for pediatric patients who received weight-based dosing for BAM (A) and ETE (B). Pediatric and adolescent BAM and ETE treatment groups were dose and weight matched within the adult 5-95th percentile range. AUC=area under the concentration versus time curve. BAM=bamlanivimab. ETE=etesevimab.

## 744 REMDESIVIR TREATMENT FOR COVID-19 IN HOSPITALIZED CHILDREN: CARAVAN INTERIM RESULTS

**Amina Ahmed**[1], Pablo Rojo[2], Allison Agwu[3], David Kimberlin[4], Jaime Deville[5], Ana Mendez-Echevarria[6], Paul Sue[7], Luisa Galli[8], Zongbo Shang[9], Kavita Juneja[9], Henry N. Hulter[9], Charlotte Hedskog[9], Kathryn Kersey[9], William Muller[10], Flor Munoz[11]

*[1]Carolinas Medical Center Levine Children's Hospital, Charlotte, NC, USA, [2]Hospital Universitario 12 de Octubre, Madrid, Spain, [3]John Hopkins Children's Center, Baltimore, MD, USA, [4]University of Alabama at Birmingham, Birmingham, AL, USA, [5]Ronald Reagan University of California, Los Angeles Medical Center, Los Angeles, CA, USA, [6]Hospital Universitario La Paz – PPDS, Madrid, Spain, [7]University of Texas Southwestern Medical Center, Dallas, TX, USA, [8]Infectious Diseases Unit, Meyer Children's University Hospital, Firenze, Italy, [9]Gilead Sciences, Inc, Foster City, CA,*

*USA, [10]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA, [11]Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA*

**Background:** Remdesivir (RDV) has been shown to shorten time to recovery in hospitalized adults with COVID-19. Some children who develop COVID-19 require hospitalization. Here we characterize the safety profile of RDV in 53 pediatric patients age 28 days to <18 years and describe clinical and virologic outcomes.

**Methods:** CARAVAN (NCT04431453) is an ongoing open-label, single arm study of RDV in hospitalized patients <18 years with PCR-confirmed COVID-19. IV RDV was given for up to 10 days: 200mg on Day 1 followed by 100mg daily in Cohort 1 and 8 (<18y, weight ≥40kg) or 5mg/kg on Day 1 followed by 2.5mg/kg daily in Cohorts 2-4 (28 days to <18y, stratified by weight). Safety was assessed by adverse events (AEs) and lab tests (hematology, chemistry, urine, inflammatory, coagulation). Clinical outcomes included improvement on a 7-point ordinal scale, time to discharge, and oxygenation modality. Virologic outcomes included days to confirmed negative SARS-CoV-2 PCR (defined as 2 consecutive negative results).

**Results:** At enrollment, median (IQR) age was 7y (2, 12) and weight was 24.6 (12.8, 55.1) Kg, 57% were female, 76% required supplemental oxygen, including 23% on invasive ventilation and 34% on high-flow oxygen (Table). Median number of RDV doses was 5 (4,8). Most patients (72%) experienced ≥1 AE; most common was constipation (17%). Serious AEs were reported for 21% of patients and none were study-drug related. Two patients with baseline transaminitis had non-serious AE of increased ALT contributing to premature discontinuation. Two patients died within the 30-day study period. Grade ≥ 3 lab abnormalities were reported in 42%; most common being decreased haemoglobin (n=9) and decreased eGFR levels (n=7). No safety trends related to RDV were apparent. In total, 85% showed clinical improvement on the 7-point ordinal scale by last assessment. Median (IQR) time to discharge was 8 (5, 17) days. By last assessment, 8% required supplemental oxygen, all of whom were invasively ventilated. Time to confirmed negative SARS-CoV-2 PCR CoV-2 PCR was 5 and 7 days from nasal/oropharyngeal samples in cohort 2 and 3, respectively, and not estimable in the other cohorts.

**Conclusion:RDV** was safe and well tolerated among children 28 days to <18y treated for COVID-19. Overall, no safety trends for RDV were apparent and a high proportion, 85%, had clinical improvement. The study is ongoing with enrolment of full term and preterm neonates pending dose determination.

**Table.**

| | Cohort 1: 2 to < 18 years and ≥ 40 kg (N= 12) | Cohort 2: 28 days to < 18 years and 20 to < 40 kg (N= 12) | Cohort 3: 28 days to < 18 years and 12 to < 20 kg (N= 12) | Cohort 4: 28 days to < 18 years and 3 to < 12 kg (N= 12) | Cohort 8: < 12 years and ≥ 40 kg (N= 5) | Total (N= 53) |
|---|---|---|---|---|---|---|
| Median age (years) (IQR) | 15 (13.5, 16.5) | 9 (7.5, 12) | 3.5 (2, 5.5) | 0.5 (0.2, 0.7) | 11 (11, 11) | 7 (2, 12) |
| Median baseline weight (kg) (IQR) | 83.5 (56.8, 106.9) | 26.5 (25, 30.9) | 14.6 (13.4, 18.2) | 5 (4.4, 8.5) | 78 (55.1, 80) | 24.6 (12.8, 55.1) |
| Median baseline BMI (kg/m2) (Q1, Q3) | 33.8 (21.6, 46.5) | 17.8 (14.9, 20.2) | 16.2 (15.6, 18.1) | 16.3 (14.7, 20) | 28 (27.2, 35.6) | 18.8 (16, 24.8) |
| Adverse Events (%) | 11 (92) | 7 (58) | 9 (75) | 7 (58) | 4 (80) | 38 (72) |
| Grade ≥3 AE | 6 (50) | 2 (17) | 1 (8) | 4 (33) | 2 (40) | 15 (28) |
| Study drug-related AE | 4 (33) | 1 (8) | 0 | 1 (8) | 2 (40) | 8 (15) |
| Serious AE | 5 (42) | 2 (17) | 0 | 3 (25) | 1 (20) | 11 (21) |
| Study-drug related SAE | 0 | 0 | 0 | 0 | 0 | 0 |
| AEs leading to discontinuation | 2 (17) | 0 | 0 | 0 | 0 | 2 (4) |
| Death during study period (%) | 1 (8) | 0* | 0 | 0 | 1 (20) | 2 (4) |
| Grade ≥3 lab abnormalities (%) | 9 (75) | 2 (17) | 4 (33) | 4 (36) | 3 (60) | 22 (42) |

*One patient (8%) from Cohort 2 experienced death outside the study period at day 32

## 745 TREATMENTS FOR MIS-C IN CHILDREN — DISCHARGE, FEVER AND SECOND-LINE THERAPIES

**Alfredo Tagarro**[1], Sara Domínguez-Rodríguez[1], Juan Miguel Mesa[2], Cristina Epalza[3], Carlos Grasa[4], María Isabel Iglesias-Bouzas[5], María Fernández-Pascual[2], Jesús Saavedra[6], Beatriz Soto[7], Jacques G. Rivière[8], Victoria Fumadó[9], Leticia Martínez-Campos[10], Álvaro Ballesteros[1], Cinta Moraleda[1]

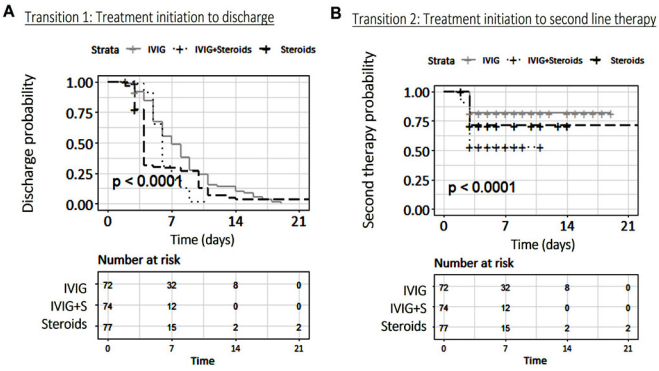
*[1]Fundación para la Investigación Biomédica del Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Spain, [3]Pediatric Research and Clinical Trials Unit (UPIC). Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain, [4]Pediatrics, Infectious and Tropical Diseases Department. Hospital Universitario La Paz. Instituto Investigación Hospital La Paz (IDIPaz), Madrid, Spain, [5]Hospital Infantil Universitario Niño Jesús, Madrid, Spain, [6]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [7]Hospital de Getafe, Getafe, Spain, [8]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [9]Hospital Sant Joan de Déu, Barcelona, Spain, [10]Hospital Universitario Torrecárdenas, Almería, Spain*

**Background:** We aimed to analyse the effects of steroids, intravenous immunoglobulin (IVIG), and their combination on the probability of discharge over time, probability of switching to second-line treatment over time, and persistent fever after 2 days of treatment.

**Methods:** We did a retrospective study to investigate the effect of treatments (IVIG plus steroids, steroids alone or IVIG alone) of children with MIS-C in a nationwide study, from 1 March to 1 June 2021. We used a Markovian multi-state model with the clock-forward approach and unidirectional arrows to build a multi-state model. Three transitions were defined: initiation of treatment to hospital discharge (t1), initiation of treatment to second-line therapy (t2), and second-line therapy to hospital discharge (t3). A treatment was considered as second-line if initiated >2 days after the first therapy. We estimated the time-to-event probability using a Cox model weighted by the propensity score to balance the baseline characteristics.

**Results:** 30/132 (22.7%) patients were initially treated with steroids alone, 29/132 (21.9%) with IVIG alone, and 73/132 (55%) with IVIG plus steroids. The probability of early discharge was higher with IVIG than with IVIG plus steroids (hazard ratio [HR] 1.65, 95% CI 1.11–2.45, p=0.013), but with a higher probability of needing second-line therapy versus IVIG plus steroids (HR 3.05, 95% CI 1.12-8.25, p=0.028). Patients on steroids had a lower probability of persistent fever after 2 days of treatment (odds ratio [OR] 0.55, 95% CI, 0.28–1.05, p=0.081) versus patients on IVIG plus steroids, and those on the combination had with a lower probability versus IVIG alone (OR 0.21, 95% CI, 0.09–0.46, p=0.0001). We also directly compared the IVig- and steroid-alone treatments. The probability of early discharge of the patients on steroids and on IVig were not different (HR 0·58, 95% CI 0·27–1·24, p=0·166). The probability of transition second-line therapy was also similar (HR 0·71, 95% CI 0·29–1·74, p=0·456). IVIG had a 4-fold higher probability of persistent fever after treatment initiation than steroids (OR 4·23 95% CI 1·43–13·5, p=0·011).

**Conclusion:** IVIG seemed to increase the probability of discharge over time but increased the probability of needing second-line treatment over time. Steroids seemed to reduce persistent fever after 2 days of treatment, and combination therapy reduced the need for escalating treatment.




## 746 ASYMPTOMATIC SARS-CoV-2 INFECTION IS EXTREMELY COMMON AMONG PEOPLE WITH HIV

**Isabelle R. Weir**[1], Edgar T. Overton[2], Markella V. Zanni[3], Stephanie Fischinger[4], Kathleen Fitch[3], Judith A. Aberg[5], Carl J. Fichtenbaum[6], Gerald S. Bloomfield[7], Carlos Malvestutto[8], Sara McCallum[1], Pamela S. Douglas[7], Galit Alter[4], Heather J. Ribaudo[1], Steven Grinspoon[3]

*[1]Harvard TH Chan School of Public Health, Boston, MA, USA, [2]University of Alabama at Birmingham, Birmingham, AL, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [5]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [6]University of Cincinnati, Cincinnati, OH, USA, [7]Duke Clinical Research Institute, Durham, NC, USA, [8]The Ohio State University, Columbus, OH, USA*

**Background:** Asymptomatic COVID-19 is common among the general population, but little has been reported on this phenomenon among people with HIV (PWH) globally. Here we present data on a representative subset of 2,464 REPRIEVE participants with blood collected for COVID-19 serology from May 2020 to February 2021.

**Methods:** REPRIEVE is an international primary atherosclerotic cardiovascular disease (ASCVD) prevention RCT of pitavastatin calcium vs. placebo among 7,770 PWH ages 40-75 on antiretroviral therapy (ART). Beginning in April 2020,

targeted data on COVID-19 diagnosis and symptoms were collected as part of routine trial visits every 4 months, and blood was collected annually to assess SARS-CoV-2 serology. SARS-CoV-2 infection was defined as either presence of SARS-CoV-2 IgG or IgA RBD protein (anti-spike) antibodies or reporting of confirmed COVID-19 disease prior to the date of antibody sampling in the absence of prior COVID-19 vaccine receipt. We distinguished symptomatic from asymptomatic disease based on completed COVID-19 symptom questionnaire. Demographic, cardiometabolic, and HIV-specific data are described among those with symptomatic versus asymptomatic COVID-19 disease.

**Results:** Participant characteristics (n=2464) included median age 53 years, 35% female sex, 47% Black or African American race, median CD4 count 649 c/$mm_3$, and 97% with HIV VL <400 cp/mL. SARS-CoV-2 infection occurred in 318 persons (13%): 58 with clinical disease diagnosis and 260 with reactive Abs but no reported clinical disease. Of these persons, 304 completed symptom questionnaires: 120 (39%) reported at least 1 symptom of COVID-19 disease, but 184 (61%) reported no symptoms. PWH with asymptomatic infection were more likely to be from non-High Income Regions, of Black or African American race, and to be non-obese (Table). Median ASCVD risk score was <5% (low risk) for the two groups. Potential differences in symptomatic disease based on ART-regimen were noted, but no clinical differences between the groups for CD4 counts or HIV viral suppression were observed.

**Conclusion:** Asymptomatic SARS-CoV-2 infection is very common among ART-treated PWH globally. With Ab testing, we determined that 61% of COVID-19 infections were asymptomatic in the REPRIEVE cohort, similar to rates reported in the general population. HIV clinicians must remain vigilant about COVID-19 testing among PWH to assure that asymptomatic cases are identified.

**Table: Characteristics* of SARS-CoV-2 Infection by Symptom Reporting**

| Characteristic | | SARS-CoV-2 Infected Symptomatic (N=120) | SARS-CoV-2 Infected Asymptomatic (N=184) | SARS-CoV-2 Uninfected (N=2146) |
|---|---|---|---|---|
| GBD Super Region | High Income | 70 (58%) | 68 (37%) | 1084 (51%) |
| | Latin America/Caribbean | 26 (22%) | 63 (34%) | 433 (20%) |
| | Southeast/East Asia | 9 (8%) | 22 (12%) | 305 (14%) |
| | South Asia | 1 (1%) | 2 (1%) | 22 (1%) |
| | Sub-Saharan Africa | 14 (12%) | 29 (16%) | 302 (14%) |
| Age (years) | | 52 (48, 57) | 53 (49, 58) | 53 (48, 57) |
| Female natal sex | | 40 (33%) | 67 (36%) | 754 (35%) |
| Race | White | 45 (38%) | 48 (26%) | 695 (32%) |
| | Black or African American | 54 (45%) | 101 (55%) | 988 (46%) |
| | Asian | 12 (10%) | 25 (14%) | 337 (16%) |
| | Other | 9 (8%) | 10 (5%) | 126 (6%) |
| Ethnicity | Hispanic or Latino | 39 (33%) | 57 (31%) | 552 (26%) |
| Obesity | BMI ≥ 30kg/m² | 48 (40%) | 40 (22%) | 511 (24%) |
| Ten year ASCVD risk (%) | | 3.7 (2.0, 5.7) | 4.8 (2.0, 7.2) | 4.1 (2.0, 6.7) |
| Smoking status | Current or Former Smoker | 53 (44%) | 71 (39%) | 988 (46%) |
| HIV-1 RNA (copies/mL) | <LLQ | 105 (88%) | 164 (91%) | 1878 (88%) |
| | LLQ to <400 | 11 (9%) | 16 (9%) | 204 (10%) |
| | ≥400 | 3 (3%) | 1 (<1%) | 48 (2%) |
| CD4 Absolute Count (cells/mm³) | | 693 (506, 879) | 584 (466, 801) | 652 (484, 854) |
| ART regimen (by class) | NRTI + INSTI | 69 (53%) | 74 (40%) | 981 (46%) |
| | NRTI + NNRTI | 33 (28%) | 69 (38%) | 699 (33%) |
| | NRTI + PI | 15 (13%) | 29 (16%) | 277 (13%) |
| | NRTI-sparing | 5 (4%) | 4 (2%) | 57 (3%) |
| | Other NRTI-containing | 4 (3%) | 8 (4%) | 132 (6%) |

**Age, BMI, HIV-1 RNA, CD4, and ART regimen are as of Jan 2020; remaining variables are as reported at study entry. Continuous variables are described as median (Q1, Q3).*

## 747 SARS-CoV-2 ANTIBODY CORRELATES AMONG PWID LIVING WITH AND WITHOUT HIV IN KENYA

**Shradha J. Doshi**[1], Hanley Kingston[1], Ashley Tseng[1], Bhavna Chohan[1], Betsy Sambai[2], Brandon Guthrie[1], Aliza Monroe-Wise[1], Loice Mbogo[3], Sarah Masyuko[3], William Sinkele[4], Paul Macharia[3], David Bukusi[2], Joshua Herbeck[1], Carey M. Farquhar[1]

*[1]University of Washington, Seattle, WA, USA, [2]Kenyatta National Hospital, Nairobi, Kenya, [3]University of Washington, Nairobi, Kenya, [4]Support for Addiction Prevention and Treatment in Africa, Nairobi, Kenya*

**Background:** In sub-Saharan Africa many persons who inject drugs (PWID) are living with undiagnosed or untreated HIV and experience high levels of poverty, housing instability, and co morbid conditions that contribute to worse outcomes from SARS-CoV-2. We sought to determine SARS-CoV-2 antibody prevalence and risk factors for PWID and their sexual and injecting partners in Kenya. Identifying the burden of infection in marginalized populations like PWID may contribute to controlling the pandemic in LMIC

**Methods:** In a nested cross-sectional study, we recruited PWID living with HIV and their injecting and/or sexual partners in Nairobi, Kilifi, and Mombasa counties at needle and syringe programs (NSP). Blood samples were collected from consenting participants at enrollment to determine SARS-CoV-2 antibodies using a Platellia BioRad SARS-CoV-2 total antibody enzyme-linked immunosorbent assay. Baseline data was collected on HIV status, antiretroviral therapy (ART) and methadone adherence. Logistic regression was used to identify factors associated with antibody positivity

**Results:** In total,1000 participants were enrolled in the study between April and July 2021, of whom 323 (32.3%) were women and 677 (67.7%) were men. Median age of participants was 36 years (Interquartile range [IQR]: 30, 42). SARS-CoV-2 positivity was reported in 309 (30.9%) of the participants. Of the participants who tested positive for SARS-CoV-2 antibodies, 39.5% did not report any symptoms at any time during the last 3 months. Men were significantly less likely than women to have SARS-CoV-2 antibodies (Odds ratio [OR] 0.70, 95% confidence interval [CI] 0.52, 0.94; p<0.016). Participants from the Coast region had lower odds of SARS-CoV-2 antibody positivity compared to the Nairobi region (OR 0.72, 95% CI, 0.54, 0.95; p<0.019) and participants who had a sexual or injecting partner diagnosed with COVID-19 were more likely to have SARS-CoV-2 antibodies detected (OR 2.12, 95% CI 1.02, 4.39; p<0.042). Living with HIV was not significantly associated with presence of SARS-CoV-2 antibodies

**Conclusion:** SARS-CoV-2 antibody was detected in 30.9% of participants in this cohort of PWID and their partners, suggesting high transmission rates within this key population. SARS-CoV-2 seroprevalence was similar for people living with and without HIV; no increase in risk was found for those living with HIV. This cohort represents an at-risk population that should be considered for COVID-19 vaccination, surveillance and other targeted public health measures

## 748 HIGHER COVID-19 POSITIVITY AND LOWER VACCINATIONS AMONG PEOPLE WHO USE DRUGS

**Javier A. Tamargo**[1], Janet Diaz-Martinez[1], Ivan Delgado-Enciso[2], Mary J. Trepka[1], David R. Brown[1], Nana A. Garba[1], Eneida Roldan[1], Yolangel Hernandez[1], Aileen M. Marty[1], Adriana Campa[1], Haley R. Martin[1], Jose A. Bastida Rodriguez[1], Yongjun Huang[1], Marianna K. Baum[1]

*[1]Florida International University, Miami, FL, USA, [2]University of Colima, Colima, Mexico*

**Background:** The COVID-19 pandemic has disproportionately impacted people who use illicit drugs and misuse prescription drugs (PWUD), including increased risk for infection with SARS-CoV-2, clinical COVID-19, and poorer health outcomes. The reasons for this disparity are multifactorial and may include numerous social and structural factors. Yet, little is known about COVID-19 testing and vaccinations among PWUD.

**Methods:** This cross-sectional study was conducted in Miami, Florida, USA between March and September 2021 with the support of the National Institutes of Health Rapid Acceleration of Diagnostics-Underserved Populations (RADx-UP) initiative. Participants had to be 18 years of age and older and willing to be tested for COVID-19. Recruitment included convenience and snowball sampling. The RADx-UP survey (available at https://radx-up.org/) was administered via telephone.

**Results:** A total of 931 participants were enrolled in the study; median age was 59 (53, 64) years, 65.5% were Black, 32.1% Hispanic, and 69.2% had a household income of less than $15,000 in 2019. Nearly a third of participants (32.6%) used drugs. Additionally, 37.6% smoked cigarettes, and 5.2% consumed alcohol for four or more days per week. Twenty percent of participants had never been tested for COVID-19. Of those who reported ever being tested, 14.1% reported ever being positive for SARS-CoV-2, with 67.2% of those having moderate-to-severe symptoms and 26.7% reporting being hospitalized due to COVID-19. Overall, 19 (2.2%) participants tested positive for SARS-CoV-2 at the time of the study, which was more frequent among PWUD than drug non-users (4.2% vs. 1.2%, respectively; p=0.004). PWUD, compared to drug non-users, were less likely to be vaccinated against COVID-19 (66.7% vs. 75.2% for any one dose, respectively; p=0.006). Compared to drug non-users, PWUD had 3.62 (95% CI: 1.41, 9.30; p=0.008) times higher odds of being positive for SARS-CoV-2 based on rt-PCR testing at the time of interview, and 0.66 (95% CI: 0.49, 0.89; p=0.006) times lower odds of being at least partially vaccinated against COVID-19.

**Conclusion:** People who use drugs may be at increased risk of contracting SARS-CoV-2 and developing COVID-19, which could be in part related to lower vaccination rates in addition to comorbidities and lifestyle factors. Testing and immunization plans are needed that are specific for PWUD, considering the barriers and facilitators of this population.

## 749 DAY-TO-DAY IMPACT OF COVID-19 ASSOCIATED WITH RISK OF OVERDOSE: 3PNO COHORT FINDINGS

**Soroush Moallef**[1], Becky L. Genberg[2], Kanna Hayashi[1], Shruti H. Mehta[2], JinCheol Choi[1], Kora DeBeck[1], Michele Kipke[3], Richard Moore[4], Marianna K. Baum[5], Steve Shoptaw[6], Pamina M. Gorbach[6], Brian Mustanski[7], Marjan Javanbakht[6], Sue Siminski[8], MJ Milloy[1]

*[1]British Columbia Centre on Substance Use, Vancouver, Canada, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]Children's Hospital Los Angeles, Los Angeles, CA, USA, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]Florida International University, Miami, FL, USA, [6]University of California Los Angeles, Los Angeles, CA, USA, [7]Northwestern University, Chicago, IL, USA, [8]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA*

**Background:** People who use unregulated drugs (PWUD) in Canada and the United States (US) are contending with the intersection of two simultaneous health crises: the COVID-19 pandemic and the longstanding drug poisoning crisis. However, the possible contributions of COVID-related factors to increases in overdoses during the pandemic are not well understood. Our study objectives were to assess the prevalence of non-fatal overdose and identify factors associated with overdose among participants in nine prospective cohorts of PWUD in urban centers in Canada (Vancouver, BC) and the US (Baltimore, MD; Miami, FL; Chicago, IL; Los Angeles, CA) during the COVID-19 pandemic. We further sought to examine the prevalence of and identify factors associated with reporting being highly impacted day-to-day by COVID-19.

**Methods:** Data were derived from the nine cohorts in the NIDA-funded C3PNO consortium between May, 2020 and April, 2021. Multivariable logistic regression was used to identify factors associated with nonfatal overdose and day-to-day impact among participants who had used unregulated drugs in the past month.

**Results:** Among 885 participants, 253 (28.6%) were female and 41 (4.6%) had reported experiencing a non-fatal overdose. Most of the sample reported being worried and approximately half reported being highly impacted day-to-day by the pandemic. In multivariable analyses, individuals who had experienced an overdose were more likely to be female (Adjusted Odds Ratio [AOR]=2.18; 95% Confidence Interval [CI]:1.10–4.30); unstably housed/homeless (AOR = 2.16; 95% CI: 1.11–4.26); engaged in medications for opioid use disorder (MOUD) (AOR = 2.45; 95% CI: 1.19–4.97); and highly impacted day-to-day by COVID-19 (AOR = 2.42; 95% CI: 1.22–5.10). In a second multivariable model, highly-impacted individuals were more likely to report higher levels of COVID-related worry (AOR = 1.30; 95% CI: 1.23–1.37) and stocking up on drugs (AOR = 1.59, 95% CI: 1.09–2.32) due to the pandemic.

**Conclusion:** Our findings indicate a need for a multi-level approach involving the spectrum of care services to meet the elevated risks of overdose in the context of the dual crises, particularly among women, those unstably housed/homeless and those who reported being highly impacted day-to-day by the pandemic. Efforts to prevent overdose, however, should prioritize addressing the root causes of the drug poisoning crisis, such as the continuous exposure to toxic and contaminated unregulated drug supplies among PWUD.

**Table 1.** Bivariable and multivariable logistic regression of factors associated with nonfatal overdose and day-to-day impact among 885 participants in nine cohorts of people who use unregulated drugs in Canada (Vancouver, BC) and the United States (Baltimore, MD; Chicago, IL; Miami, FL; Los Angeles, CA), May 2020 to April, 2021.

| | Multivariable model 1* | | | | Multivariable model 2* | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | Unadjusted Odds Ratio (95% CI) | *P* value | Adjusted Odds Ratio (95% CI) | *P* value | Unadjusted Odds Ratio (95% CI) | *P* value | Adjusted Odds Ratio (95% CI) | *P* value |
| Age (per year) | 1.01 (0.98 - 1.03) | 0.578 | 1.00 (0.98 - 1.03) | 0.792 | 0.99 (0.98 - 1.00) | 0.004 | 0.98 (0.97 - 0.99) | 0.001 |
| White (vs non-white) | 1.11 (0.56 - 2.10) | 0.758 | — | — | 0.95 (0.72 - 1.25) | 0.712 | 1.55 (1.10 - 2.18) | 0.012 |
| Female (vs male) | 0.49 (0.26 - 0.94) | 0.029 | 2.18 (1.10 - 4.30) | 0.024 | 0.71 (0.53 - 0.95) | 0.021 | 0.78 (0.55 - 1.09) | 0.139 |
| Unstably housed/homeless (vs. house/apartment)[a] | 0.45 (0.24 - 0.85) | 0.014 | 2.16 (1.11 - 4.26) | 0.024 | 1.06 (0.80 - 1.39) | 0.695 | 1.37 (1.00 - 1.89) | 0.055 |
| Sexual partners[a] (per partner) | 1.04 (0.98 - 1.10) | 0.113 | 1.06 (0.99 - 1.12) | 0.054 | 1.04 (0.99 - 1.09) | 0.155 | — | — |
| In MOUD[a] | 2.27 (1.18 - 4.28) | 0.012 | 2.45 (1.19 - 4.97) | 0.013 | 0.60 (0.44 - 0.82) | 0.001 | 0.64 (0.44 - 0.92) | 0.015 |
| Nonfatal overdose[a] | — | — | — | — | 2.39 (1.23 - 4.93) | 0.013 | 2.60 (1.25 - 5.71) | 0.013 |
| Daily drug use[a]: | | | | | | | | |
| Alcohol | 1.12 (0.33 - 2.90) | 0.828 | — | — | — | — | — | — |
| Opioid[b, c] | 1.40 (0.64 - 2.82) | | — | — | 1.00 (0.63 - 1.60) | 0.986 | — | — |
| Stimulants[b, d] | 1.53 (0.74 - 2.98) | 0.231 | — | — | 1.00 (0.71 - 1.40) | 0.999 | — | — |
| Injection drug use | 1.95 (1.03 - 3.67) | 0.038 | — | — | 0.87 (0.63 - 1.20) | 0.389 | — | — |
| COVID-19 related factors[a]: | | | | | 0.83 (0.63 - 1.10) | 0.199 | — | — |
| Tested for COVID-19 | 1.46 (0.79 - 2.69) | 0.391 | 2.00 (0.98 - 4.28) | 0.063 | | | 1.52 (1.08 - 2.14) | 0.015 |
| COVID-19 worry[e] | 1.01 (0.93 - 1.11) | 0.543 | — | — | 1.91 (1.45 - 2.52) | <0.001 | 1.30 (1.23 - 1.37) | <0.001 |
| Highly impacted day-to-day[f] | 2.39 (1.23 - 4.93) | 0.013 | 2.42 (1.22 - 5.10) | 0.015 | — | — | — | — |
| Avoided needle distribution sites | 2.28 (0.90 - 5.04) | 0.058 | 2.00 (0.75 - 4.72) | 0.135 | 1.09 (0.69 - 1.76) | 0.705 | — | — |
| Avoided picking up MOUD[a] | 0.63 (0.04 - 3.07) | 0.658 | — | — | 0.79 (0.39 - 1.58) | 0.503 | 0.51 (0.24 - 1.11) | 0.088 |
| Stocked up on drugs | 1.07 (0.45 - 2.25) | 0.869 | — | — | 1.68 (1.19 - 2.39) | 0.003 | 1.59 (1.09 - 2.32) | 0.016 |

*Model 1 = factors associated with non-fatal overdose; Model 2 = factors associated with reporting being highly impacted day-to-day by the pandemic
CI: Confidence interval. MOUD: medication for opioid use disorder
[a] Denotes behaviours and events in the past month.
[b] Injection or non-injection drug use.
[c] Refers to any heroin, fentanyl, or prescription opioid use
[d] Refers to any methamphetamine, powder or crack cocaine use
[e] Derived from asking participants to rate on a scale ranging from 1 (not at all worried) to 10 (very much worried) how worried they are about the COVID-19 pandemic
[f] Derived from asking participants to rate on a scale (not at all, a little, much, very much, extremely) how much/did the COVID-19 pandemic impact their day-to-day life (highly impacted vs. moderate to no impact)

## 750 SEROPREVALENCE AND RISK FACTORS FOR SARS-CoV-2 AMONG INCARCERATED ADULT MEN IN QUEBEC

**Nadine Kronfli**[1], Camille Dussault[2], Mathieu Maheu-Giroux[3], Alexandros Halavrezos[2], Sylvie Chalifoux[2], Jessica P. Sherman[2], Hyejin Park[2], Lina Del Balso[1], Matthew P. Cheng[1], Sebastien Poulin[4], Joseph Cox[1]

*[1]McGill University Health Centre, Montreal, Canada, [2]McGill University Health Centre Research Institute, Montreal, Canada, [3]McGill University, Montreal, Canada, [4]Centre intégré de santé et de services sociaux des Laurentides, Montreal, Canada*

**Background:** People in prison are at increased risk of SARS-CoV-2 infection due to overcrowding and the challenges in implementing infection prevention and control measures; however, seroprevalence studies are lacking in correctional settings. We examined the seroprevalence of SARS-CoV-2 and associated modifiable risk factors among incarcerated adult men in Quebec, Canada.

**Methods:** We conducted a cross-sectional seroprevalence study in three provincial prisons, representing 45% of Quebec's incarcerated male provincial population. The primary outcome was SARS-CoV-2 antibody seropositivity, detected by the Roche Elecsys® anti-SARS-CoV-2 serology test. Participants completed self-administered questionnaires on sociodemographic, clinical, and carceral characteristics. The association of carceral variables with SARS-CoV-2 seropositivity was examined using Poisson regression models with robust standard error. Crude and adjusted prevalence ratios (aPR) with 95% confidence intervals (95%CI) were calculated.

**Results:** Between January 19 and September 15, 2021, 246 of 1,100 (22%) recruited individuals tested positive across three prisons (range 15-27%). Of these, 192 (78%) reported having at least one previous SARS-CoV-2 PCR test, with 122 (64%) testing positive and 70 (36%) testing negative; 73 (30%) individuals with a positive serology test were asymptomatic. Seropositivity increased with time spent in prison since March 2020 (aPR 2.17, 95%CI 1.53–3.07 for all vs. little), employment during incarceration (aPR 1.64, 95%CI 1.28–2.11 vs. not), shared meal consumption during incarceration (with cellmates: aPR 1.46, 95%CI 1.08–1.97 vs. alone; with sector: aPR 1.34, 95%CI 1.03–1.74 vs. alone), and incarceration post-prison outbreak (aPR 2.32, 95% CI 1.69–3.18 vs. pre-outbreak) (see Table). Shared (vs. single) cells were not associated with increased seropositivity.

**Conclusion:** The seroprevalence of SARS-CoV-2 among incarcerated individuals was high and varied between prisons. Several modifiable carceral factors were associated with seropositivity, underscoring the importance of decarceration and occupational safety measures, individual meal consumption, and enhanced infection prevention and control measures including vaccination during incarceration.

| Models | Carceral exposures | aPR | 95% CI |
|---|---|---|---|
| Model 1[a] | **Time spent incarcerated since March 2020** | | |
| | Little (<10%) | *Reference* | |
| | Some (10-49%) | 1.32 | 0.95-1.85 |
| | Most (50-99%) | **1.47** | **1.01-2.12** |
| | All (100%) | **2.17** | **1.53-3.07** |
| Model 2[b] | **Room type** | | |
| | Single cells | *Reference* | |
| | Shared cells | 1.03 | 0.77-1.36 |
| Model 3[c] | **Employed during incarceration** | | |
| | No | *Reference* | |
| | Yes | **1.64** | **1.28-2.11** |
| Model 4[d] | **Meal consumption** | | |
| | Alone | *Reference* | |
| | Cellmates | **1.46** | **1.08-1.97** |
| | Sector | **1.34** | **1.03-1.74** |
| Model 5[e] | **Time of incarceration at screening** | | |
| | Pre-outbreak | *Reference* | |
| | Post-outbreak | **2.32** | **1.69-3.18** |

aPR = adjusted prevalence ratio; CI = confidence interval
[a]Adjusted for age, race/ethnicity, education, housing status, provincial prison, and employment status during incarceration.
[b]Adjusted for medical comorbidities, provincial prison, employment status during incarceration, and time of incarceration at screening.
[c]Adjusted for age, education, medical comorbidities and provincial prison.
[d]Adjusted for COVID-19 symptoms, provincial prison, room type, employment status during incarceration, and time of incarceration at screening.
[e]Adjusted for age, medical comorbidities, provincial prison, room type, meal consumption, and employment status during incarceration.

## 751 RACIAL/ETHNIC AND NEIGHBORHOOD SOCIAL VULNERABILITY DISPARITIES IN COVID-19

**Usama Bilal**[1], Florence Momplaisir[2], Alina Schnake-Mahl[1], Kathleen Murphy[2], John Jemmott[2]

*[1]Drexel University, Philadelphia, PA, USA, [2]University of Pennsylvania, Philadelphia, PA, USA*

**Background:** To describe disparities by race/ethnicity and neighborhood social vulnerability in COVID-19 positivity, hospitalization, and mortality.

**Methods:** Longitudinal cohort study based on electronic health records (EHR) of all individuals tested for COVID-19 in the University of Pennsylvania Hospital System (UPHS) or hospitalized with confirmed COVID-19 infection in five UPHS hospitals from March 1, 2020, to March 31, 2021. Exposures: Race/ethnicity as

documented in the EHR and neighborhood-level social vulnerability index. Main outcomes: COVID-19 test positivity, hospitalization with COVID-19, and 30-day in-hospital mortality following hospitalization with COVID-19.

**Results:** A total of 225,129 unique individuals (58% White, 25% Black, 5% Hispanic, and 5% Asian) received COVID-19 testing and 5,794 unique patients (38% White, 43% Black, 9% Hispanic, 5% Asian) were hospitalized with COVID-19. During the first wave (March-June 2020), and compared to whites, all racial/ethnic minority groups had higher test positivity, especially Blacks (aOR=2.80, 95% CI 2.62-2.99) and Hispanics (aOR=4.22, 95% CI 3.85-4.62); residents of high (aOR=2.39, 95% CI 2.09-2.74) and medium (aOR=1.19, 95% CI 1.03-1.37) social vulnerability neighborhoods had higher test positivity than those living in low social vulnerability neighborhoods. These associations were sustained during second and subsequent waves. We also found higher odds of hospitalization for racial/ethnic minorities (74%, 82%, and 68% higher among Blacks, Hispanics, and Asians, as compared to whites, during the first wave, and 108%, 81% and 53% higher during the second and subsequent waves) and individuals living in high social vulnerability neighborhoods (34% and 85% higher compared to low social vulnerability during the first and second and subsequent waves). For positivity and hospitalization, we also found significant interactions between race/ethnicity and social vulnerability, although the direction of these interactions varied by race/ethnicity. We did not see clear in-hospital mortality disparities during the first wave and observed 75% and 68% higher odds of death among Hispanic and Asians during the second and subsequent waves, as compared to Whites.

**Conclusion:** We observed significant racial/ethnic and neighborhood disparities in COVID-19 outcomes, especially test positivity and odds of hospitalization, highlighting the importance of reducing inequities in exposure to SARS-CoV-2.

**Table: Odds ratios (95% CI) of testing positivity, hospitalization, and in-hospital mortality associated with race/ethnicity and neighborhood-level social vulnerability considered separately, by wave**

| | | Testing Positivity (OR, 95% CI) | | Hospitalization (OR, 95% CI) | | In-hospital Mortality (OR, 95% CI) | |
|---|---|---|---|---|---|---|---|
| | Category | 1st Wave | 2nd+ Wave | 1st Wave | 2nd+ Wave | 1st Wave | 2nd+ Wave |
| Race Ethnicity | NH White | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| | NH Black | **2.8 (2.62-2.99)** | **1.57 (1.49-1.65)** | **1.74 (1.48-2.05)** | **2.08 (1.84-2.35)** | 0.88 (0.63-1.22) | 1.1 (0.79-1.54) |
| | Hispanic | **4.22 (3.85-4.62)** | **2.17 (2.01-2.35)** | **1.82 (1.46-2.26)** | **1.81 (1.51-2.16)** | 0.76 (0.42-1.38) | **1.75 (1.01-3.02)** |
| | NH Asian | **1.61 (1.42-1.82)** | **1.44 (1.32-1.57)** | **1.68 (1.24-2.28)** | **1.53 (1.25-1.87)** | 1.08 (0.59-1.98) | **1.68 (1.01-2.79)** |
| | NH Other | **2.4 (2.11-2.74)** | **1.73 (1.56-1.92)** | 0.73 (0.49-1.07) | 1.09 (0.83-1.42) | 1.21 (0.55-2.66) | 1.52 (0.67-3.45) |
| | Missing | **2.31 (2.06-2.6)** | **1.32 (1.2-1.46)** | **0.33 (0.22-0.51)** | **0.48 (0.34-0.69)** | 1.27 (0.49-3.26) | **3.86 (1.82-8.17)** |
| | p-val* | <0.001 | | 0.108 | | 0.186 | |
| Social Vulnerability | Low | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| | Medium | **1.19 (1.03-1.37)** | 1.08 (0.95-1.23) | 0.91 (0.68-1.22) | 1.23 (0.96-1.57) | 0.99 (0.67-1.46) | 1.08 (0.76-1.54) |
| | High | **2.39 (2.09-2.74)** | **1.67 (1.47-1.89)** | **1.34 (1.02-1.74)** | **1.85 (1.46-2.34)** | 0.95 (0.65-1.39) | 1.05 (0.73-1.51) |
| | p-val* | <0.001 | | 0.005 | | 0.903 | |

**Footnote: models control for age, age², sex, and hospital (for in-hospital mortality). Race/ethnicity and SVI results come from different models. Testing positivity refers to the odds of ever testing positive; hospitalization refers to the odds of being hospitalized 2 weeks prior or 4 weeks after the first positive test; in-hospital mortality refers to the odds of dying in-hospital by 30 days after admission with a COVID-19 confirmed flag. *p-val refers to the p-value for interaction between wave and race/ethnicity or SVI.**

## 752 ASSOCIATION BETWEEN THE NEIGHBORHOOD BUILT ENVIRONMENT AND COVID-19 HOSPITALIZATION

**Sarah E. Rowan**[1], Alessandro Rigolon[2], Jeremy Nemeth[3], Cory Hussain[1], Brian Montague[4], Brenn Anderson-Gregson[3], Priyanka deSouza[3], Kristine Erlandson[4]
*[1]Denver Health and Hospital Authority, Denver, CO, USA, [2]University of Utah, Salt Lake City, UT, USA, [3]University of Colorado Denver, Denver, CO, USA, [4]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** The COVID-19 pandemic has been marked by its disparate impacts on residents in lower income neighborhoods. To better understand reasons for disparities in disease severity, we asked: To what extent does the neighborhood built environment independently predict COVID-19 hospitalizations for people with SARS-CoV-2?

**Methods:** Retrospective analysis of all cases of SARS-CoV-2 diagnosed within the University of Colorado Health and Denver Health healthcare systems from 3/1/2020 – 12/15/2020. Electronic health records were queried for positive SARS-CoV-2 PCR results for individuals aged ≥18 years during the study period. Demographic and health variables were extracted. Home addresses were matched with social vulnerability indices and built environment variables including population density and crowding, environmental hazards and amenities, and mobility options. Logistic regression was used to identify factors of the neighborhood built environment associated with hospitalization after a positive SARS-CoV-2 result.

**Results:** Among the two systems, 39,304 individuals had positive SARS-CoV-2 tests; 14,604 (37.16%) had full demographic data; 4,101 (28%) were hospitalized. Odds of hospitalization were higher for individuals living in apartments and in census blocks with lower residential density and higher percentage of multi-family housing units. See Table. Higher particulate matter (PM2.5) levels were associated with higher odds of being hospitalized but living within ¼ mile of a highway was not. Living within 1/2 mile of a park and more park acreage in the neighborhood were associated with lower odds of hospitalization. Odds of being hospitalized were higher for individuals in neighborhoods with a lower Walk Score ®, lower Bike Score ®, and higher Transit Score ®. Effects were more pronounced for Latinx individuals.

**Conclusion:** Among those with SARS-CoV-2 infection in Denver, living in areas with high levels of PM2.5, less park access, and lower Walk® and Bike Scores® were found to be independent risk factors for hospitalization when controlling for income and medical comorbidities.

*Table 1. Odds ratios of hospitalization after a positive SARS-CoV-2 test result by neighborhood built environment characteristics*

| | All cases [a] | | Latinx [a] | | Non-Hispanic White [b] | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | Odds ratio | 95% CI | Odds ratio | 95% CI |
| Residential density | **0.999*** | 0.9998-0.9999 | **0.9998*** | 0.9997-0.9999 | 0.9999 | 0.9998-1.0000 |
| Living in a multi-family building | **1.153**** | 1.036-1.282 | 1.139^ | 0.981-1.321 | 1.154 | 0.950-1.400 |
| Percent multi-family units | **1.306*** | 1.006-1.694 | **2.576***** | 1.749-3.795 | 0.913 | 0.599-1.387 |
| PM 2.5 | **1.324***** | 1.194-1.467 | **1.453***** | 1.212-1.744 | **1.239**** | 1.080-1.425 |
| Proximity to a highway | 1.063 | 0.967-1.168 | 1.0007 | 0.867-1.155 | 1.123 | 0.970-1.299 |
| Park access | **0.848***** | 0.778-0.923 | **0.752***** | 0.666-0.849 | 0.965 | 0.835-1.114 |
| Park acreage | **0.228***** | 0.102-0.504 | 0.334^ | 0.104-1.053 | **0.264*** | 0.071-0.963 |
| Walk Score ® | **0.995**** | 0.992-0.998 | 0.996 | 0.991-1.001 | 0.996 | 0.991-1.001 |
| Bike Score ® | **0.992***** | 0.987-0.996 | **0.984***** | 0.978-0.990 | 0.997 | 0.990-1.003 |
| Transit Score ® | **1.006**** | 1.001-1.010 | **1.013***** | 1.006-1.020 | **1.008**** | 1.002-1.014 |

PM2.5=levels of particulate matter ≤2.5 microns in width. Odds ratios in bold are significant at the 0.05 level. ^ $p < 0.10$; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. [a] Spatial filtering models. [b]Not spatially adjusted model. All models are adjusted by age, gender, race, ethnicity, BMI, comorbid medical conditions, and significant built environment variables.

## 753 A NATIONAL SEROPREVALENCE SURVEY OF SARS-CoV-2 ANTIBODIES IN SOUTH AFRICA: 2020-2021

**Leickness C. Simbayi**[1], Sizulu Moyo[1], Adrian Puren[2], Penny Moore[3], Samuel Manda[4], Nompumelelo Zungu[1], Khangelani Zuma[1], Edmore Marinda[1], Sean Jooste[1], Tarylee Reddy[5], Lynn Morris[2], Ameena Goga[4], Musawenkosi Mabaso[1], Whadi-ah Parker[1], Inbarani Naidoo[1]
*[1]Human Sciences Research Council, Pretoria, South Africa, [2]National Institute for Communicable Diseases, Johannesburg, South Africa, [3]University of the Witwatersrand, Johannesburg, South Africa, [4]South African Medical Research Council, Cape Town, South Africa, [5]South African Medical Research Council, Durban, South Africa*

**Background:** South Africa is one of the African countries most affected by the COVID-19 pandemic. SARS-CoV-2 seroprevalence surveys provide valuable epidemiological information given the existence of asymptomatic cases. We report the findings of the first nationwide household-based population estimates of SARS-CoV-2 seroprevalence among people aged 12 years and older in South Africa.

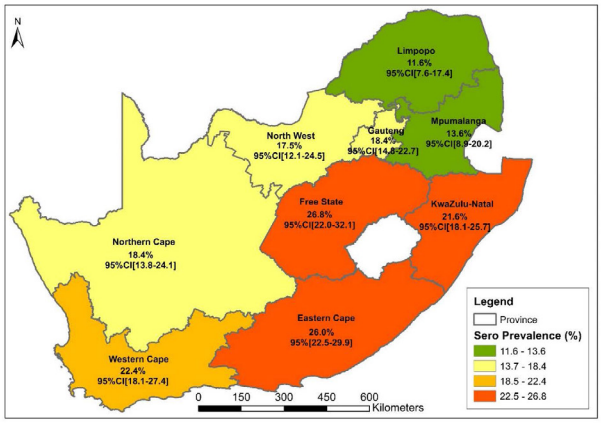
**Methods:** The survey used a cross-sectional multi-stage stratified cluster design undertaken over two separate time periods (November 2020 - February 2021 and April - June 2021) which coincided with the second and third waves of the pandemic in South Africa. The Abbott® and Euroimmun® ani-SARS CoV-2 antibody assays were used to test for SARS-CoV-2 antibodies, the latter being the final result. The survey data was weighted with final individual weights benchmarked against 2020 mid-year population estimates by age, race, sex, and province. Frequencies were used to describe characteristics of the study population and SARS-CoV-2 seroprevalence. Bivariate and multivariate logistics regression analysis were used to identify factors associated with SARS-CoV-2 seropositivity.

**Results:** 13640 participants gave a blood sample. The SARS-CoV-2 seroprevalence using the Euroimmun assay was 19.6% (95% CI 17.9–21.3) over the study period, translating to an estimated 8 675 265 (95% CI 7 508 393 – 9 842 137) estimated infections among people aged 12 years and older across South Africa by June 2021. Seroprevalence was higher in the Free State (26.8%), and Eastern Cape (26.0%) provinces (Figure). Increased odds of seropositivity were associated with prior PCR testing [aOR=1.29 (95% CI: 0.99-1.66)], being female [aOR=1.28 (95% CI 1.00-1.64), p=0.048] and hypertension, [aOR=1.28 (95% CI 1.00-1.640, p=0.048].

**Conclusion:** These findings highlight the burden of infection in South Africa by June 2021, and support testing strategies that focus on individuals with known exposure or symptoms since universal testing is not feasible. Females and younger people were more likely to be infected suggesting need for additional strategies targeting these populations. The estimated number of infections was 6.5 times higher than the number of SARS-CoV-2 cases reported nationally, suggesting that the country's testing strategy and capacity partly explain the

dynamics of the pandemic. It is therefore essential to bolster testing capacity and to rapidly scale up vaccinations in order to contain the spread of the virus in the country.

***Figure: SARS CoV-2 seroprevalence by province among population 12 years and older, South Africa, 2021***




## 754 LOCAL-SCALE SPATIAL VARIABILITY IN SARS-CoV-2 SEROPREVALENCE IN AN INDIAN MEGACITY

**Eshan U. Patel**[1], Rifa Khan[2], Matt Hitchings[3], Aylur K. Srikrishnan[2], Mark Anderson[4], K. S. Kumar[2], Amy Wesolowski[1], Syed H. Iqbal[2], Mary A. Rodgers[4], Shruti H. Mehta[1], Gavin Cloherty[4], Derek A. Cummings[3], Sunil S. Solomon[5]
*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]YR Gaitonde Center for AIDS Research and Education, Chennai, India, [3]University of Florida, Gainesville, FL, USA, [4]Abbott Labs, Abbott Park, IL, USA, [5]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** While the diversity in SARS-CoV-2 transmission across geographies and risk groups is well recognized, there has been limited investigation into spatial heterogeneity at a local scale, that is variability across a single city. Identifying patterns and factors associated with spatial variability requires population representative samples which are challenging to obtain but critical for mitigation strategies including vaccine distribution.
**Methods:** From Jan to May 2021, we sampled 4,828 participants from 2,723 unique households across 100 spatial locations in Chennai, India using a probability proportional to population density sampling approach. All participants provided a blood sample and underwent a household and individual survey. 4,712 samples were tested for antibodies to the Spike protein (anti-Spike IgG) by the Abbott ARCHITECT. SARS-CoV-2 prevalence by spatial location was plotted using splines estimated by generalized additive models. Associations between seroprevalence and spatial attributes (zone, population density), study characteristics (date of sampling), household and individual-level covariates were estimated using Bayesian mixed effects logistic regression accounting for clustering within households and locations.
**Results:** The median age was 38 and 49% self-identified as female. Overall, anti-S IgG prevalence was 61.9% (95% confidence interval [CI]: 60.5-63.3%) but ranged from 41.5% to 73.1% across the 12 zones. Splines indicated statistically significant variation in seroprevalence across the city (Panel A). Mixed effects regression including location and household effects indicated 31% of variance was attributable to location. In adjusted analysis, seroprevalence was significantly associated with population density (OR=1.46 per 100 people/100 sq meter [95%CI: 1.08-1.97]; Panel B), age (OR=1.004 [95%CI: 1.0002-1.005]), having an air conditioner (OR=0.65 [95%CI: 0.43-0.98]) and sample timing but not with household crowding (OR=0.97 per person/room [95%CI: 0.75-1.26]; Panel C). Significant spatial variation across locations remained after adjustment for these variables, accounting for 28% of variance.
**Conclusion:** We observed substantial spatial heterogeneity of SARS-CoV-2 burden in this high prevalence setting not fully explained by individual, household or population factors. Such local variability in prevalence has implications not only for transmission but for scale-up of vaccines which remain in limited supply in low- and middle-income countries.

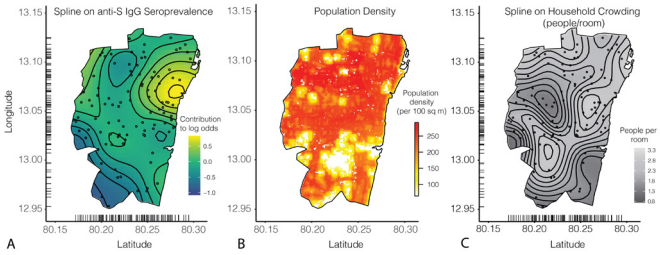



**Figure. Local-scale spatial variation in (A) anti-Spike IgG seroprevalence, (B) population density, and (C) household crowding.**

## 755 PHYLODYNAMIC OF SARS-CoV-2 TRANSMISSION IN FRANCE: 2020

**Romain Coppée**[1], François Blanquart[1], Aude Jary[2], Valentin Leducq[2], Anna-Maria Franco-Yusti[1], Léna Daniel[1], Charlotte Charpentier[2], Karen Zafilaza[3], Vincent Calvez[2], Diane Descamps[2], Anne Genevieve Marcelin[2], Benoît Visseaux[2], Antoine Bridier-Nahmias[1]
*[1]Institut National de la Santé et de la Recherche Médicale, Paris, France, [2]Assistance Publique–Hôpitaux de Paris, Paris, France, [3]Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France*

**Background:** In 2020, France reported 2.7 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), making it the second most affected European country by the COVID-19 pandemic after the United Kingdom. However, dynamics of SARS-CoV-2 transmissions within France or between France and other countries remains partially characterized. We propose an analysis of these dynamics on multiple scales, from the continents to the French administrative regions.
**Methods:** We produced 736 SARS-CoV-2 sequences from Ile-de-France (Paris area, France) and analyzed them concomitantly with GISAID deposited sequences to elucidate the origins and spread of the virus from January 2020 to December 2020. A total of 4,571 worldwide sequences, including 1,652 French sequences, constituted the final dataset. All sequences were selected to be representative of each country temporal distribution of SARS-CoV-2 to the week resolution. We used a maximum likelihood phylogenetic framework to estimate the most probable temporal and geographic spread of SARS-CoV-2 within France and worldwide. Depending on the geographical focus (France, Europe or worldwide), we pruned the tree accordingly in 1,000 independent replicates.
**Results:** Phylogenetic analysis revealed that, during the 1st French epidemic wave (from March to May), the majority of viruses introduced to France came from North America (USA) and Europe (Spain, Italy, …). France regularly transmitted to neighboring European countries: Belgium, Germany, Italy and United Kingdom. Contrary to the 1st wave, inter-country transmission events were limited to neighboring countries and intercontinental transmission were almost absent during the French 2nd wave (from September to November). At the French regions-scale, we observed that Ile-de-France (IDF) was the main source of infections for all other French regions during the 1st epidemic wave, with a minor participation of Provence-Alpes-Côte d'Azur (PACA). For the 2nd epidemic wave, PACA was the main source of infections for all other French regions, with a lower participation of IDF and other regions.
**Conclusion:** Overall, our findings allow a more comprehensive representation of SARS-CoV-2 transmission chains related to and within France and the global temporal distribution of those events, in link with control measures applied during the whole 2020 period. IDF and PACA were the main hubs of transmissions in France for the 1st and the 2nd epidemic waves, respectively.

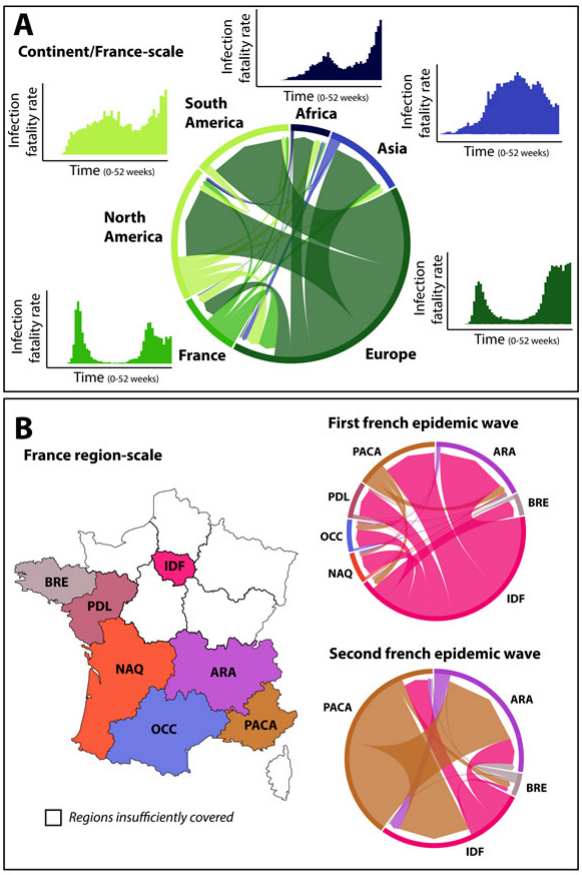



***Figure.*** Transitions events, obtained by phylogeographic reconstruction of SARS-CoV-2 molecular diversity in 2020, between continents throughout 2020 (panel A) and between French regions during the first and second French epidemic waves (panel B). Sequences have been selected to reflect the SARS-CoV-2 epidemiology (panel A).

## 756 MAIN SARS-CoV-2 CIRCULATING VARIANTS IN SPAIN DURING THE FIRST YEAR OF THE PANDEMIC

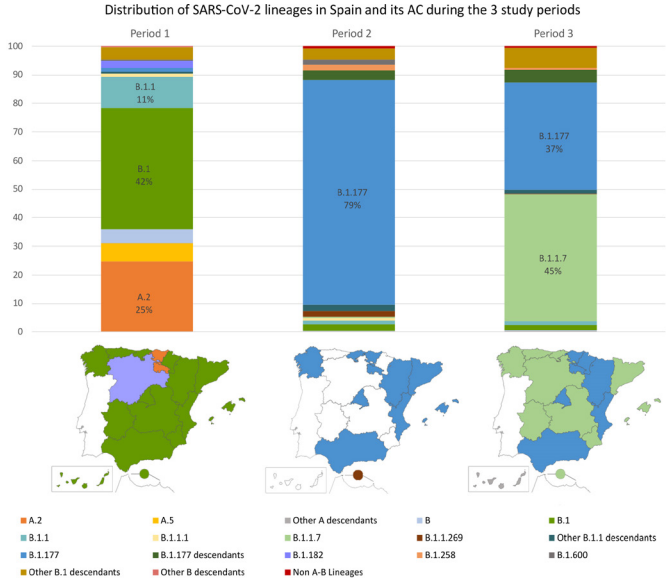
**Paloma Troyano-Hernáez**[1], Roberto Reinosa[1], África Holguín[1]
[1]*Hospital Ramón y Cajal, Madrid, Spain*

**Background:** Spain has been one of the main epicenters for Covid-19 in Europe. The country is divided into 17 Autonomous Communities (AC) and two Autonomous Cities (ACi). This study aims to describe the epidemiology of SARS-CoV-2 in Spain across 3 study periods established from the beginning of the pandemic to the third epidemiologic wave, after analyzing genomes from all AC/ACi from February 2020 to March 2021.

**Methods:** All 14,256 available partial and complete Spanish SARS-CoV-2 human genomic sequences deposited in the GISAID repository (https://www.gisaid.org/) until 21 March 2021 were downloaded in nucleotides and classified according to the AC/ACi and to the epidemiological week by collection date. The sequences were assigned to the genetic lineages according to Pangolin COVID-19 Lineage Assigner (https://pangolin.cog-uk.io/). Epiweeks were grouped into three main periods adjusted to the Spanish epidemic curve, as informed in the National Epidemiological Surveillance Network (RENAVE, https://cnecovid.isciii.es). The first period comprised from the beginning of the pandemic to the end of the first state of emergency (June 2020). The second period included the second epidemic wave (June-December 2020), and the third period covered the third wave (December 2020-March 2021). Only AC with at least 10 sequences for each period were described in the results. The two ACi were considered together.

**Results:** Before the national lockdown (14 March 2020), 11 SARS-CoV-2 lineages were circulating in Spain with A.2 lineage predominance. During the lockdown the SARS-CoV-2 variant diversity increased, decreasing during the confinement. During this period, B.1 was the main circulating variant. During summer 2020, B.1.177 became the main circulating variant. The third wave was characterized by the introduction and fast spread of the B.1.1.7 or Alpha Variant of Concern.

**Conclusion:** The reduction of diversity during the lockdown suggests this measure was effective in reducing the import of SARS-CoV-2 lineages. After the opening of borders within Europe during summer 2020, the variant diversity increased again and B.1.177 became the predominant variant, suggesting that despite the efforts to avoid SARS-CoV-2 spread between countries, travel restrictions during summer 2020 were not sufficient to control viral spreading. The variant distribution was heterogeneous among the AC and periods, reflecting different incidence and sequencing capacities across AC.




## 757 MOLECULAR EPIDEMIOLOGY OF THE COVID-19 PANDEMIC IN CHICAGO

**Ted Ling Hu**[1], Lacy M. Simons[1], Egon A. Ozer[1], Ramon Lorenzo-Redondo[1], Judd F. Hultquist[1]
[1]*Northwestern University, Chicago, IL, USA*

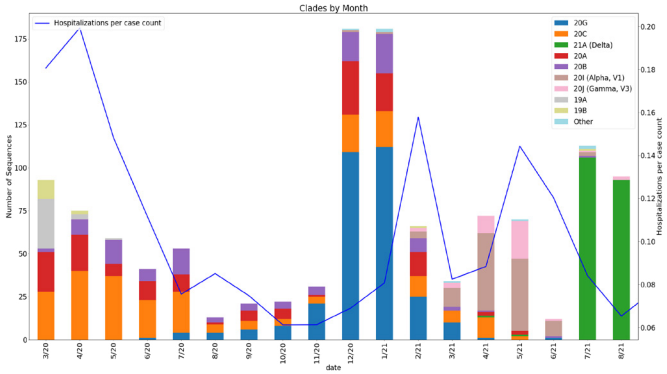
**Background:** The greater Chicagoland area has recorded over 10,000 COVID-related deaths and nearly 600,000 cases since the start of the COVID-19 pandemic in March of 2020. SARS-CoV-2, the causative agent of COVID-19, has continually changed over that time, with some variants evolving to become more transmissible or more resistant to neutralizing antibody responses.

**Methods:** To better understand how viral genetic variation has contributed to differences in COVID-19 pathogenesis and patient outcome, we established a biobank of residual diagnostic samples from adult patients who tested positive for COVID-19 in a PCR-based test at Northwestern Memorial Hospital. Thus far, we have collected samples from 6448 out-patients and 632 in-patients. Of these, we have performed whole genome sequencing and viral load calculations on 1373 samples. Clinical and demographic information, including composite measures of disease severity, were extracted from available electronic health records. These data were assessed for longitudinal patterns and for specific association with viral lineage.

**Results:** We found that the early epidemic in March of 2020 was defined by three distinct lineages reflecting the outbreaks in China (19B/A), Washington state (19B/A.1), and New York state (19A/B.1). By November of 2020, we saw a large increase in the number of confirmed cases, dominated by the 20G clade. This lineage remained predominant until March of 2021, when the Alpha and Gamma variants of concern became more established. These were recently supplanted by the Delta variant, which now accounts for over 90% of Chicago cases. At the height of the pandemic in November of 2020, case counts peaked at over 5000 cases per day, but hospitalizations, ICU admissions, and deaths over this period remained flat. Statistical testing revealed that the predominant clade at that time, 20G, was associated with better outcomes and less severe disease as measured by clinical measures of patient deterioration, even when controlling for patient demographics. These results suggest that a viral variant associated with less severe disease was predominant in late 2020 before the emergence of the more transmissible variants of concern.

**Conclusion:** Current work is being done to determine if the less severe outcomes associated with this clade also contributed to more asymptomatic transmission, potentially contributing to the high case counts recorded over this

period. These data emphasize the need for continued genomic surveillance of SARS-CoV-2 to character.




## 758 CHARACTERISTICS AND OUTCOMES CHANGES IN COVID-19 INPATIENTS : A COMPARISON OF 4 WAVES

**Martin Martinot**[1], Magali Eyriey[1], Simon Gravier[1], Ciprian Ion[1], Mahsa Mohseni-Zadeh[1], Estelle Rougier[1], Jean-Claude Ongagna[1], Anais Henric[1], Anne Schieber[1], Christian Kempf[1]

[1]*Hôpital Civil de Colmar, Colmar, France*

**Background:** Four Coronavirus disease 2019 (COVID-19) epidemic waves occurred in France between March 2020 and September 2021. These 4 waves had different intensities and anti severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) therapies including the extensive use of corticosteroids, monoclonal antibodies, high-flow nasal oxygenotherapy, and generalization of vaccination. This single-center retrospective study compared patients' characteristics and outcomes during these four waves.

**Methods:** We retrospectively analyzed the data of all consecutive inpatients with proven COVID-19 (based on polymerase chain reaction (PCR) testing of nasopharyngeal swab sampling) in a French tertiary care hospital from March 1 to July 31, 2020 (wave 1), August 1 to December 31 (wave 2), January 1 to June 30, 2021 (wave 3), and August 1 to September 30, 2021 (wave 4). Differences in baseline characteristics and outcomes i.e., intensive care unit (ICU) hospitalization and deaths were assessed. A patient with healthcare-associated COVID-19 was defined by a positive PCR 48 h after admission. Continuous variables were compared using the Kruskal–Wallis test and categorical data by the Chi-square test (SAS 9.4 software).

**Results:** During wave 1, 1939 patients were hospitalized at the HCC for COVID-19 816 (42.1%), 463 (23.9%) during wave 2, 572 (29.5%) during wave 3, and 88 (4.5%) during wave 4. Table 1 summarizes the patients' main clinical characteristics, baseline biological results, and outcome according to COVID-19 waves Results are presented in table 1 in the form n (%) [95% confidence interval], percentages are calculated for non missing values only. Wave 1 patients were hospitalized later after COVID-19 symptom onset, had more serious disease at baseline (higher temperature, more frequent need for oxygen, higher C-reactive protein and lactate dehydrogenase levels, and lower lymphocytes), and were more frequently hospitalized in the ICU. Wave 4 patients were younger. The highest death rates were found during the first 2 waves; 17% vs. 15% in wave 3 and 4% in wave 4. A higher percentage of healthcare-associated COVID-19 was found in wave 2. Although the month of October was not included in the results, there was a marked decrease of cases and the lowest death rate during wave 4.

**Conclusion:** Wave 1 patients were had more serious disease at baseline with the highest death and ICU hospitalization rates. Deaths were reduced during wave 3 and 4 with a marked decrease in the number of patients hospitalized during wave 4.

| | Wave 1 (n = 816) | Wave 2 (n = 463) | Wave 3 (n = 572) | Wave 4 (n = 88) | All patients (n = 1939) | p-value |
|---|---|---|---|---|---|---|
| Gender (Male) | 454 (55.6%) | 249 (53.8%) | 317 (55.7%) | 45 (51.1%) | 1065 (54.9%) | 0.807 [4] |
| Age (years) | | | | | | |
| Median [Q1, Q3] | 71.34 [60.3;81.8] | 76.22 [62.4;85.6] | 71.27 [57.7;83.1] | 52.74 [29,3;71.6] | 71.90 [58.8;83.0] | <0.001 [1] |
| BMI (kg/m²) | | | | | | |
| Median [Q1, Q3] | 26.56 [23.37;30.80] | 25.76 [22.22;29.71] | 26.29 [23.17;30.39] | 25.69 [19.65;29.26] | 26.22 [22.84;30.40] | 0.043 [1] |
| Risk factor(s) | 710 (87.3%) | 412 (89.4%) | 516 (90.8%) | 61 (70.1%) | 1699 (88.1%) | <0.001 [4] |
| Chronic renal disease | 78 (9.6%) | 80 (17.4%) | 88 (15.4%) | 7 (8.0%) | 253 (13.1%) | <0.001 [4] |
| Chronic liver disease | 10 (1.2%) | 16 (3.5%) | 13 (2.3%) | 1 (1.1%) | 40 (2.1%) | 0.06 [4] |
| Chronic cardio-vascular | 553 (68.0%) | 314 (68.1%) | 400 (70.2%) | 37 (42.5%) | 1304 (67.5%) | <0.001 [4] |
| Chronic pulmonary disease | 166 (20.4%) | 121 (26.2%) | 177 (31.1%) | 23 (26.4%) | 487 (25.2%) | <0.001 [4] |
| Diabetes | 209 (25.7%) | 133 (28.9%) | 160 (28.1%) | 13 (14.9%) | 515 (26.7%) | 0.03 [4] |
| Cancer | 156 (19.2%) | 128 (27.8%) | 142 (24.9%) | 10 (11.5%) | 436 (22.6%) | <0.001 [4] |
| immunosuppression | 11 (1.4%) | 5 (1.1%) | 19 (3.3%) | 3 (3.4%) | 38 (2.0%) | 0.025 [4] |
| Pregnancy | 2 (0.2%) | - | 4 (0.7%) | 2 (2.3%) | 8 (0.4%) | 0.029 [4] |
| Neurologic disorders | 150 (18.5%) | 115 (24.9%) | 120 (21.1%) | 10 (11.5%) | 395 (20.5%) | 0.006 [4] |
| Symptoms duration (days) | | | | | | |
| Median [Q1, Q3] | 6.0 [9;2] | 3.0 [7;1] | 4.0 [8;0] | 5.5 [9;2] | 5.0 [9;1] | <0.001 [1] |
| Body temperature (°C) | | | | | | |
| Median [Q1, Q3] | 37.9 [36.8;38.5] | 37.0 [36.4;38.0] | 37.1 [36.4;38.0] | 36.9 [36.4;37.5] | 37.30 [36.6;38.2] | <0.001 [1] |
| Ventilation | | | | | | |
| Spontaneous ambient air | 485 (64.0%) | 302 (69.7%) | 369 (70.6%) | 49 (65.3%) | 1205 (67.4%) | 0.055 [4] |
| Lymphocytes (G/L) Median [Q1, Q3] | 0.790 [0.54;1.13] | 0.840 [0.57;1.29] | 0.900 [0.62;1.36] | 1.020 [0.61;1.67] | 0.840 [0.57;1.23] | <0.001 [1] |
| CRP (mg/L) Median [Q1, Q3] | 71.0 [31;127] | 39.0 [11;85] | 45.0 [13;107] | 27.0 [4;93] | 23.0 [4;93] | <0.001 [1] |
| LDH (IU/L) Median [Q1, Q3] | 310.0 [228;428] | 253.5 [201;307] | 259.0 [200;348] | 300.0 [197;389] | 274.0 [210;364] | <0.001 [1] |
| ICU hospitalization (%) | 183 (22.4%) | 56 (12.1%) | 90 (15.7%) | 11 (12.5%) | 340 (17.5%) | <0.001 [4] |
| Deaths (%) | 140 (17.2%) | 81 (17.5%) | 88 (15.4%) | 4 (4.5%) | 313 (16.1%) | 0.004 [4] |

## 759 EFFICACY OF NATURAL IMMUNITY AGAINST REINFECTION WITH SARS-CoV-2 B.1.351 VARIANT

**Laith J. Abu-Raddad**[1], Hiam Chemaitelly[1]

[1]*Weill Cornell Medicine College in Qatar, Doha, Qatar*

**Background:** Reinfections with emerging SARS-CoV-2 variants are a serious concern. This study estimated the efficacy of immunity induced by natural infection against reinfection with B.1.351 and B.1.1.7 variants.

**Methods:** Two retrospective matched cohort studies were conducted in Qatar from March 8-April 21 to assess reinfection in the national cohort of individuals with a prior PCR-confirmed infection and the national cohort of antibody-positive individuals, matching each in a 1:1 ratio by demographic characteristics to the national cohort of antibody-negative individuals. Incidence risks (using the Kaplan-Meier estimator), incidence rates, and efficacy of natural infection against reinfection were estimated.

**Results:** In the study comparing 44,821 individuals with a prior PCR-confirmed infection to antibody-negative individuals, the efficacy of natural infection against reinfection was 92.3% (95% CI: 90.3-93.8%) for B.1.351, 97.6% (95% CI: 95.7-98.7%) for B.1.1.7, and 87.9% (95% CI: 84.7-90.5%) for unidentified variants (mostly suspected B.1.351 cases based on weekly sequencing analysis). In the second study, comparing 20,406 antibody-positive to antibody-negative individuals, efficacy was 86.4% (95% CI: 82.5-89.5%) for B.1.351, 96.4% (95% CI: 92.1-98.3%) for B.1.1.7, and 83.1% (95% CI: 77.2-87.5%) for unidentified variants. Additional analyses and sensitivity analyses confirmed these results, albeit with slightly lower efficacies.

**Conclusion:** Natural infection with SARS-CoV-2 induces robust protection of 80-90% against reinfection with B.1.351 even a year after the primary infection, but lower than that against B.1.1.7.

## 760 CLINICAL OUTCOME IN PEOPLE WITH COVID-19 BY HIV-STATUS: A NATIONWIDE REGISTER STUDY

Late Breaking

**Isabela Möller**[1], Magnus Gisslen[2], Philippe Wagner[3], Pär Sparén[1], Anders Sönnerborg[1], Christina Carlander[1]

[1]*Karolinska Institute, Stockholm, Sweden,* [2]*Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden,* [3]*Lund University, Lund, Sweden*

**Background:** It is still unclear whether people with HIV (PWH) are more likely to have severe outcome of COVID-19. We aimed to assess this association using nation-wide register data.

**Methods:** We included all adults hospitalized with a primary diagnosis of COVID-19 (ICD-10; U07.1, U07.2) in Sweden between Feb 1, 2020, and Aug 31, 2021, identified from the National Patient Register. The study population was linked to the National HIV Quality Register (n= 8 032), the Swedish Intensive Care Register, the Swedish Cause of Death Register, and the LISA database for labour market studies. Using multivariate logistic regression models, we estimated adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for severe COVID-19 (intensive care admission or 90-day mortality), by HIV-status.

**Results:** We included 121 PWH and 64 764 HIV-negative individuals hospitalized with COVID-19. PWH were younger (median age 57y vs. 65y, p<0.001) and more likely to be men (68% vs. 57%, p=0.015) compared to HIV-negative. There was no difference in level of education, level of income or number of comorbidities. Most hospitalized PWH had undetectable HIV-RNA (93%) and high CD4 counts (median 560, IQR 376-780). Severe COVID-19 was identified in 17 (14%) PWH and 14 648 (23%) HIV-negative. Ten (8%) PWH and 10 217 (16%) HIV-negative died within 90 days. HIV status was not associated

with higher odds of severe COVID-19 (aOR 0.88, 95% CI 0.52-1.49). Higher age was associated with severe COVID-19 in PWH (aOR 1.08, 95% CI 1.02-1.15). PWH with one or more comorbidities were four times more likely to have severe COVID-19 (aOR 4.3, 95% CI 1.1-16.7, ref PWH with no comorbidity). Neither level of income nor level of education or migrant status was associated with severe COVID-19 in PWH. Level of HIV-RNA, current CD4, nadir CD4, and mode of HIV-transmission was not associated with severe COVID-19. PWH admitted to the ICU were six times more likely treated with tocilizumab compared to HIV-negative admitted to the ICU (aOR 6.1, 95% CI 1.5-24.5), even after adjusting for regional differences in early adoption of tocilizumab use. There was no difference in the number treated with steroids (aOR 0.9, 95% CI 0.2-3.1).

**Conclusion:** This nation-wide cohort study, including the entire Swedish adult population hospitalized with COVID-19, indicates that PWH with well-treated HIV-infection have similar odds of severe COVID-19 as HIV-negative individuals. PWH admitted to the ICU were more likely treated with tocilizumab compared to HIV-negative.

**Table 1. Characteristics of people hospitalized with COVID-19**

| | Patients with HIV | Patients without HIV | P-value |
|---|---|---|---|
| **All, n** | 121 | 64 764 | |
| Sex<br>Men, n (%) | 82 (68) | 36 711 (57) | **0.015** |
| Age<br>Median (IQR) | 57 (47-64) | 65 (51-78) | **<0.001** |
| ≥65 years, n (%) | | | |
| **Level of education, n (%)** | | | 0.930 |
| <9 years | 32 (26) | 18 483 (28) | |
| 10-12 years | 52 (43) | 26 459 (41) | |
| >12 years | 33 (28) | 17 297 (27) | |
| Missing | 4 (3) | 2 525 (4) | |
| **Annual income ($), n (%)** | | | 0.252 |
| < 11 000 | 15 (12) | 6 376 (10) | |
| 11 000-22 000 | 40 (33) | 20 716 (32) | |
| 22 001-33 000 | 19 (16) | 14 617 (23) | |
| > 33 000 | 47 (38) | 22 706 (35) | |
| Missing | - | 349 (0.5) | |
| **Comorbidities, n (%)** | | | |
| Cancer | 4 (3) | 3,166 (5) | 0.423 |
| Cerebrovascular disease | 3 (3) | 2,118 (3) | 0.626 |
| Chronic heart disease | 14 (12) | 8,353 (13) | 0.664 |
| Chronic kidney disease | 6 (5) | 3,291 (5) | 0.951 |
| Chronic lung disease | 13 (11) | 8,501 (13) | 0.439 |
| Diabetes mellitus | 23 (19) | 12,622 (19) | 0.894 |
| Disease of the nervous system | 8 (7) | 6,209 (10) | 0.270 |
| Hepatic disease | 1 (1) | 99 (0.2) | 0.093 |
| Hypertension | 23 (19) | 21,567 (33) | **0.001** |
| Immunodeficiency | 3 (2) | 829 (1) | 0.250 |
| Inflammatory disease | - | 617 (1) | - |
| Obesity | 2 (2) | 3,781 (6) | 0.067 |
| **Number of comorbidities, n (%)** | | | 0.083 |
| 0 | 64 (53) | 26 344 (41) | |
| 1 | 28 (23) | 16 445 (25) | |
| 2 | 16 (13) | 12 015 (18) | |
| 3 | 8 (7) | 6 121 (9) | |
| ≥4 | 5 (4) | 3 839 (6) | |
| **HIV-related characteristics** | | | |
| **Year of HIV-diagnosis, n (%)** | | | |
| 1979-2000 | 48 (50) | - | |
| 2001-2010 | 44 (36) | - | |
| 2011-2021 | 29 (24) | - | |
| **Mode of HIV transmission, n (%)** | | | |
| Heterosexual | 60 (50) | - | |
| MSM/bisexual | 37 (31) | - | |
| IVDU | 12 (10) | - | |
| Blood products | 2 (1.6) | - | |
| Mother to child | 1 (0.8) | - | |
| Other or unknown | 9 (7) | - | |
| **Born outside Sweden** | 79 (65) | | |
| **Nadir CD4 (cells/mL), median (IQR)** | 142 (50-290) | - | |
| **Current CD4 count (cells/mL) median (IQR)** | 560 (376-781) | - | |
| **Current CD4 count ≤ 200 (cells/mL), n (%)** | 7 (6) | | |
| **Peak HIV-RNA ever (copies/mL) median (IQR)** | 155 000<br>(359 000-695 000) | | |
| **Current viral suppression (≤50copies/mL), n (%)** | 113 (93) | | |

Calculated using logistic regression analyses. Significant results in bold. Percentages does not always add up to 100% due to rounding. Abbreviations: COVID-19 = Corona virus disease -19, HIV = Human immunodeficiency virus, ICU = Intensive care unit, IQR = Interquartile range, IVDU = Intravenous drug use, MSM = Men who have sex with men, Severe COVID-19 = defined as admission to ICU or 90-day mortaliity

## 761 LIFE EXPECTANCY AFTER HIV DIAGNOSIS 2008–2018, USA

**Azfar-E-Alam Siddiqi**[1], Anna Satcher Johnson[1], Angela Hernandez[1], Xiaohong Hu[1], Ruiguang Song[1]
[1]*Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** Life expectancy among persons with diagnosed HIV has continued to improve, particularly since introduction of antiretroviral treatment. Building on our previous work we update the life expectancy estimates for an 11-year period from 2008–2018.

**Methods:** We used National HIV Surveillance Data on persons ≥13 years old at HIV diagnosis, to estimate life expectancy after HIV diagnosis following the life table approach. Survival within the first year, or beyond first year after HIV diagnosis were estimated separately to estimate overall life expectancy. Estimates were also generated separately by sex at birth, race/ethnicity (Black, Hispanic/Latino or White persons), disease severity (stage 3 vs all other stages), and transmission category. The data were statistically adjusted for missing risk factors.

**Results:** In 2018, the life expectancy of persons with HIV diagnosis was 32.85 years (95% CI 32.80–32.90), representing an increase of 4.3 years from 28.63 years (95% CI, 28.58–28.67) in the year 2008. In 2018, the Life expectancy was higher for males; 32.70 (95%CI 32.64-32.75) than females; 29.58 (95%CI 29.48-29.69). Over the 11-year period life expectancy improved for all persons by age-groups, sex at birth, race/ethnicity, transmission category, and stage of disease at diagnosis, though the improvements were not uniform across all groups.

**Conclusion:** Consistent increases in life expectancy among people with diagnosed HIV during 2008–2018 were observed, though disparities by sex and by race/ethnicity persist.

Table: Life expectancy in persons with diagnosed HIV, years 2008–2018; overall and by sex at birth and race/ethnicity.

| | | Male | | | Female | | |
|---|---|---|---|---|---|---|---|
| Year of HIV diagnosis | *Overall* | Black/African American | Hispanic/ Latino | White | Black/African American | Hispanic/ Latino | White |
| 2008 | *28.63* | 26.81 | 32.69 | 26.95 | 26.25 | 30.73 | 26.70 |
| 2009 | *29.31* | 27.87 | 33.24 | 27.40 | 26.54 | 30.94 | 27.76 |
| 2010 | *30.41* | 29.16 | 33.88 | 28.02 | 27.37 | 31.95 | 27.87 |
| 2011 | *30.97* | 29.94 | 34.34 | 28.15 | 28.17 | 31.73 | 27.68 |
| 2012 | *31.52* | 30.37 | 35.30 | 28.47 | 28.12 | 32.26 | 27.60 |
| 2013 | *31.83* | 30.89 | 35.18 | 28.32 | 28.34 | 32.25 | 28.02 |
| 2014 | *32.35* | 31.49 | 35.48 | 28.87 | 28.72 | 32.99 | 28.79 |
| 2015 | *32.65* | 31.64 | 35.69 | 29.15 | 28.76 | 33.81 | 28.79 |
| 2016 | *32.67* | 31.71 | 35.99 | 29.17 | 28.78 | 31.97 | 28.78 |
| 2017 | *32.68* | 31.50 | 35.67 | 29.51 | 28.90 | 33.08 | 28.31 |
| 2018 | *32.85* | 31.53 | 35.55 | 29.56 | 29.08 | 32.24 | 28.25 |

## 762 SURVIVAL AMONG HIV-POSITIVE VETERANS BEFORE AND AFTER THE VA OPT-OUT TESTING POLICY

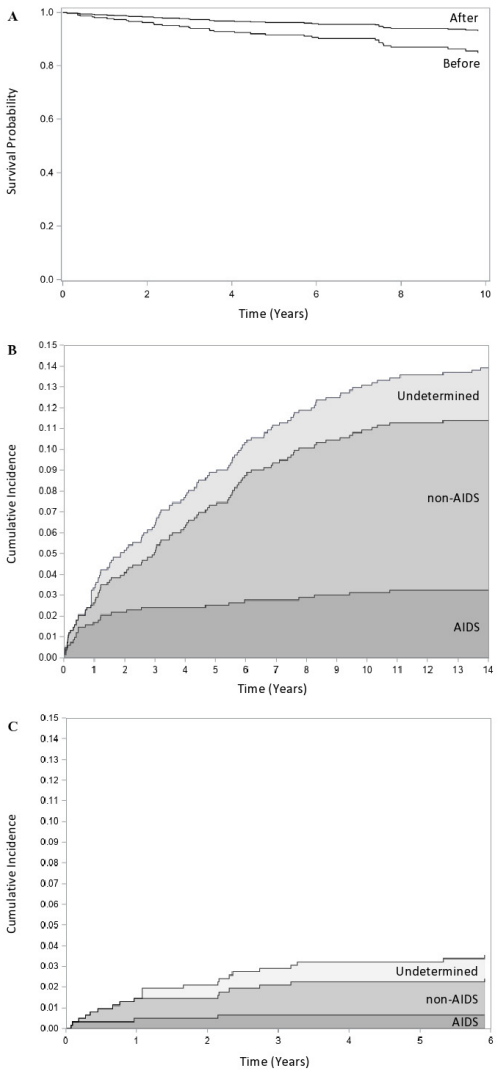
**Kartavya J. Vyas**[1], Vincent Marconi[1], Jodie L. Guest[1]
[1]*Emory University, Atlanta, GA, USA*

**Background:** The VA is the largest provider of HIV care in the U.S.; however, up to 3% of VA patients were undiagnosed with HIV and most were diagnosed with AIDS at the time of their HIV diagnosis. To improve early detection and linkage to care, the VA began to offer opt-out HIV testing, with verbal, rather than written, informed consent, as of August 17, 2009.

**Methods:** The HIV Atlanta VA Cohort Study (HAVACS) is a cohort of all HIV-positive veterans at the Atlanta VA Medical Center; analyses were restricted to those who were diagnosed with HIV in the late-HAART era and before the end of the study period (2002-2016). Bivariate analyses examined significant differences in CD4 counts at HIV diagnosis and ART initiation, time before first HIV clinic visit, and ages at HIV and AIDS diagnoses. Survival curves, adjusted for CD4 count at ART initiation, and cumulative incidence functions were estimated for all-cause and cause-specific mortality, respectively. Poisson regression models estimated rate ratios for all-cause and cause-specific mortality, adjusted for CD4 count at ART initiation.

**Results:** Of 1,465 HAVACS patients who contributed 9,577 PY, 844 (58%) and 621 (42%) were diagnosed with HIV before and after the policy, respectively; of whom, 118 (14%) and 22 (4%) died, respectively. Patients diagnosed with HIV after the policy had statistically significantly greater mean (SD) CD4 counts at HIV diagnosis (432 [290] vs. 331 [262] cells/mL) and ART initiation (352 [265] vs. 180 [160] cells/mL), and lower median (IQR) days between HIV diagnosis and first HIV clinic visit (78 [81] vs. 164 [508] days). Moreover, patients diagnosed with HIV after the policy had a lower mean (SD) age at HIV diagnosis (40.7 [13.5] vs. 41.2 [11.8]) and a higher mean (SD) age at AIDS diagnosis (48.7 [13.1] vs. 46.6 [10.9]). The adjusted 10-year cumulative survival increased from 84% before to 93% after the policy. After the policy, adjusted rates (IRR [95% CI]) of all-cause (0.8 [0.5, 1.2]), AIDS- (0.7 [0.2, 1.9]), and non-AIDS-related (0.8 [0.4, 1.3]) mortality decreased.

**Conclusion:** VA patients after the policy were diagnosed with HIV at an earlier age, had greater CD4 counts at HIV diagnosis and ART initiation, reduced time to first HIV clinic visit, were diagnosed with AIDS at a later age, had an increased 10-year cumulative survival, and lower rates of mortality. The results may provide a valuable impetus for other large healthcare organizations seeking to expand HIV testing.



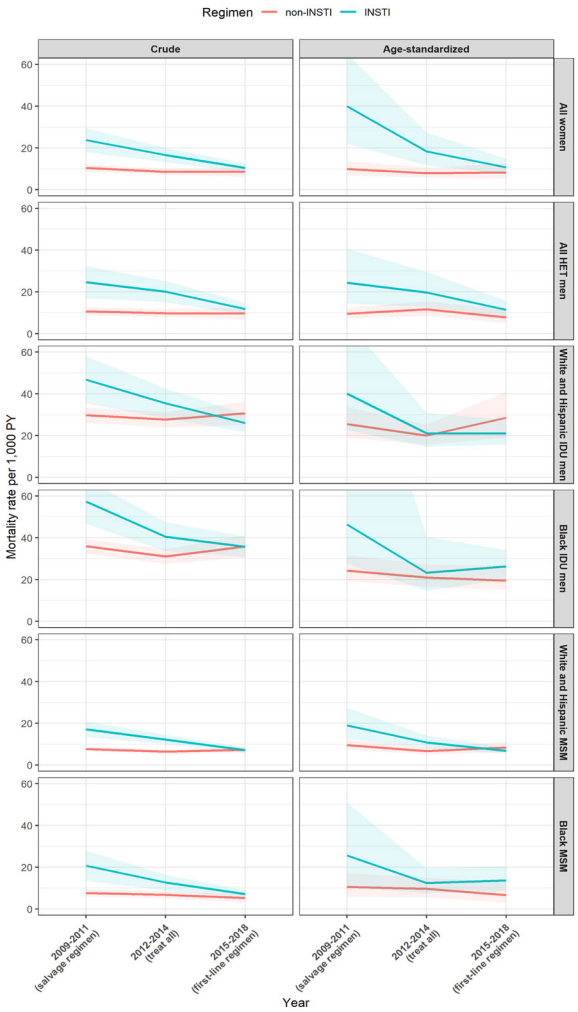

**Estimates of adjusted survival probability and cumulative incidence of mortality in HIV-infected veterans (n=1,465). A,** KM survival curves, adjusted for CD4 count at ART initiation, of all-cause mortality among veterans diagnosed with HIV before and after the VA opt-out testing policy on August 15, 2009. **B**, stacked CIF plots of undetermined, non-AIDS- and AIDS-related mortality before policy (n=118). **C**, stacked CIF plots of undetermined, non-AIDS- and AIDS-related mortality after policy (n=22). AIDS, acquired immune deficiency syndrome; CIF, cumulative incidence function; HIV, human immunodeficiency virus; KM, Kaplan-Meier.

## 763 MORTALITY RATES WITH OR WITHOUT InSTI THERAPY IN SUBGROUPS OF PWH: 2009-2018

**Keri N. Althoff**[1], Elizabeth Humes[1], Parastu Kasaie[1], Cameron Stewart[1], Emily P. Hyle[2], Peter F. Rebeiro[3], Katherine Kooij[4], Maile Y. Karris[5], Vincent Marconi[6], Ank Nijhawan[7], Marina B. Klein[8], M. John Gill[9], Joseph J. Eron[10], Richard Moore[11]
*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Vanderbilt University, Nashville, TN, USA, [4]University of British Columbia, Vancouver, Canada, [5]University of California San Diego, San Diego, CA, USA, [6]Emory University, Atlanta, GA, USA, [7]University of Texas Southwestern, Dallas, TX, USA, [8]McGill University Health Centre, Montreal, Canada, [9]University of Calgary, Calgary, Canada, [10]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [11]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** In 2009, integrase strand transfer inhibitors (InSTIs) were used as a salvage regimen. In 2014, InSTIs became the guideline-recommended regimen for initiation (i.e., first-line). Following our report of declining mortality among people receiving HIV care in the NA-ACCORD, we investigated mortality by InSTI use from 2009-2018.
**Methods:** Adults (≥18 years) prescribed ART in NA-ACCORD clinical cohorts contributed deaths and person-time from 2009-2018. Age-adjusted mortality rates (MRs) and 95% confidence intervals ([,]) were estimated by direct standardization to the 2000 U.S. Standard Population. Quasi-Poisson regression accounted for overdispersion and produced age-adjusted MR ratios (aMRRs) by time-updated InSTI use (vs. non-InSTI use) within sex-and-HIV acquisition risk and race/ethnicity subgroups: women, heterosexual men, white and Hispanic men with a history of injection drug use (IDU), Black men with IDU, white and Hispanic men who have sex with men (MSM), and Black MSM. All analyses were stratified by calendar period: 2009-2011 (salvage period), 2012-2014 (treat all onset), and 2015-2018 (first-line regimen period). Each subgroup had ≥20 deaths in both InSTI and non-InSTI groups in each period.
**Results:** A total of N=60,728 ART users contributed 4,355 deaths and 291,013 person-years from 2009-2018, of whom 50% (n=30,357) used an InSTI regimen. The MR among those receiving InSTIs decreased dramatically over time as their use evolved from salvage to the first-line regimen (2009-2011: MR=32.0 [26.1, 38.7], 2012-2014: MR=16.8 [14.5, 19.3], and 2015-2018: MR=13.5 [12.0, 15.0]). These declines were muted for non-InSTI users (2009-2011: MR=15.4 [13.9, 17.1], 2012-2014: MR=13.0 [11.7, 14.5], and 2015-2018: MR=13.3 [11.6, 15.1]), and patterns were consistent among subgroups (Figure). In 2015-2018, there was no mortality difference comparing InSTI to non-InSTI users overall in the adjusted model (aMRR=1.00 [0.95, 1.04]); this was true of all subgroups except Black MSM (aMRR=1.35 [1.06, 1.72]).
**Conclusion:** With the evolution of InSTIs from a salvage to a first-line regimen from 2009-2018, the overall mortality has decreased substantially among individuals receiving InSTIs. In the period of InSTIs as a first-line regimen (2015-2018), we found no difference in mortality by InSTI use except among Black MSM. Mortality differences within some subgroups merit investigation to determine drivers of heterogeneties and appropriate interventions to narrow disparities.

**Figure 1:** Crude and direct age-standardized mortality rates (line) and 95% confidence intervals (shaded region) among those using ART with an INSTI-based regimen (vs. anothe regimen) from 2009-2018, among a) women (N=11,309), b) heterosexual men (N=8,082), c) White and Hispanic men with IDU (N=5,757), d) Black men with IDU (N=6,427), e) Whit and Hispanic men who have sex with men (MSM, N=20,358), and f) Black MSM (N=8,795)



## 764 ASSOCIATIONS OF MODERN INITIAL ANTIRETROVIRAL DRUG REGIMENS WITH ALL-CAUSE MORTALITY

**Adam Trickey**[1], Lei Zhang[1], Suzanne M. Ingle[1], Antonella Castagna[2], Piotr Cichon[3], Pere Domingo[4], Sophie Grabar[5], Mina Psichogiou[6], Marta Rava[7], Peter Reiss[8], Christopher T. Rentsch[9], Melchor Riera[10], Michael J. Silverberg[11], Caroline Sabin[12], Jonathan A. Sterne[1]

*[1]University of Bristol, Bristol, UK, [2]University vita E. Salute, Milan, Italy, [3]Otto-Wagner Hospital, Vienna, Austria, [4]Santa Creu i Sant Pau Hospital, Barcelona, Spain, [5]Sorbonne University, Paris, France, [6]National and Kapodistrian University of Athens, Athens, Greece, [7]Institute of Health Carlos III, Madrid, Spain, [8]Stichting HIV Monitoring, Amsterdam, Netherlands, [9]London School of Hygiene & Tropical Medicine, London, UK, [10]Hospital Son Espases, Mallorca, Spain, [11]Kaiser Permanente, Oakland, CA, USA, [12]University College London, London, UK*

**Background:** Regimens including integrase strand inhibitors (InSTIs) are now the most commonly used for persons with HIV (PWH) starting antiretroviral therapy (ART). Trials and observational studies have compared virological failure on InSTI-based with other regimens, but few data are available on mortality among PWH treated with InSTIs in routine care.

**Methods:** We compared virological suppression (≤50 copies/mL) and all-cause mortality between different InSTI- and non-InSTI-based regimens among PWH starting ART in Europe and North America from 2013-18 in 21 cohorts participating in the Antiretroviral Therapy Cohort Collaboration and the UK Collaborative HIV Cohort Study. We studied the most used 'third' antiretroviral drugs during 2013-18: rilpivirine, darunavir, raltegravir, elvitegravir, dolutegravir and efavirenz. Adjusted hazard ratios (aHRs) were estimated using Cox models with terms for clinical and demographic characteristics, co-morbid conditions (hepatitis C, hepatitis B, AIDS- and non-AIDS defining cancers, cardiovascular events, and AIDS events), and other drugs in the regimen, stratified by cohort and ART start year (2013-15, 2016-2018), as predictors of ART regimen choice evolved rapidly between 2013 and 2018.

**Results:** Of 62,500 ART-naïve PWH starting ART (20% female; median age 38), 1,243 died during 188,952 person-years follow-up (median 3.0 years). Rates of virological suppression were higher for regimens with dolutegravir than other third drugs, and for raltegravir than rilpivirine, darunavir, or efavirenz. There was little evidence that mortality rates differed between regimens with dolutegravir, elvitegravir, rilpivirine, darunavir, or efavirenz as third drugs. However, mortality was higher for raltegravir compared with dolutegravir (aHR 1.49 [95%CI: 1.15-1.94]), elvitegravir (1.86 [1.43-2.42]), rilpivirine (1.99 [1.49-2.66]), darunavir (1.62 [1.33-1.98]), and efavirenz (2.12 [1.60-2.81]) (see table). Results were similar for analyses making different assumptions about missing data and consistent between the two ART start year periods.

**Conclusion:** This large study found little evidence that mortality rates differed between PWH receiving most first-line ART regimens. However, those receiving raltegravir-based regimens experienced higher mortality. Unmeasured confounding may explain our findings. Virological benefits of first-line integrase strand inhibitors-based ART may not translate to differences in mortality.

**Table:** Hazard ratios (95% confidence intervals) for mortality and time to viral suppression for each 3rd drug comparison, using multiple imputation to account for missing data

| Comparison of 3rd drugs | Mortality | Time to viral suppression |
|---|---|---|
| DRV vs DTG | 0.98 (0.77-1.25) | 0.60 (0.58-0.62) |
| DRV vs EVG | 1.17 (0.92-1.50) | 0.68 (0.65-0.70) |
| DRV vs RPV | 1.19 (0.91-1.57) | 0.98 (0.95-1.01) |
| EFV vs DTG | 0.75 (0.53-1.07) | 0.64 (0.61-0.67) |
| EFV vs EVG | 0.87 (0.64-1.18) | 0.72 (0.69-0.75) |
| EFV vs RPV | 0.93 (0.68-1.27) | 1.05 (1.01-1.09) |
| EVG vs DTG | 0.79 (0.60-1.05) | 0.88 (0.85-0.92) |
| RAL vs DRV | 1.62 (1.33-1.98) | 1.31 (1.25-1.37) |
| RAL vs DTG | 1.49 (1.15-1.94) | 0.78 (0.74-0.82) |
| RAL vs EFV | 2.12 (1.60-2.81) | 1.22 (1.16-1.29) |
| RAL vs EVG | 1.86 (1.43-2.42) | 0.89 (0.84-0.93) |
| RAL vs RPV | 1.99 (1.49-2.66) | 1.28 (1.22-1.35) |
| RPV vs DTG | 0.78 (0.55-1.10) | 0.61 (0.59-0.63) |
| RPV vs EVG | 0.93 (0.68-1.28) | 0.69 (0.66-0.72) |

Rilpivirine (RPV), Darunavir (DRV), Raltegravir (RAL), Elvitegravir (EVG), Dolutegravir (DTG), Efavirenz (EFV).

## 765 REDUCTIONS IN MORTALITY RISK AFTER STARTING ART IN 2010-2019 VERSUS 1995-2003

**Lei Zhang**[1], Suzanne M. Ingle[1], M. John Gill[2], Ard van Sighem[3], Robert Zangerle[4], Enrico Girardi[5], Matthias Cavassini[6], Greer Burkholder[7], Derek D. Satre[8], George Adamis[9], Amy Justice[10], Sophie Grabar[11], John Koethe[12], Heidi Crane[13], Jonathan A. Sterne[1]

*[1]University of Bristol, Bristol, UK, [2]University of Calgary, Calgary, Canada, [3]Stichting HIV Monitoring, Amsterdam, Netherlands, [4]Innsbruck Medical University, Innsbrusk, Austria, [5]Istituto Nazionale Malattie Infettive L. Spallanzani, Rome, Italy, [6]Lausanne University Hospital, Lausanne, Switzerland, [7]University of Alabama at Birmingham, Birmingham, AL, USA, [8]University of California San Francisco, San Francisco, CA, USA, [9]Gennimatas General Hospital, Athens, Greece, [10]Yale University, New Haven, CT, USA, [11]Sorbonne University, Paris, France, [12]Aalborg University Hospital, Aalborg, Denmark, [13]University of Washington, Seattle, WA, USA*

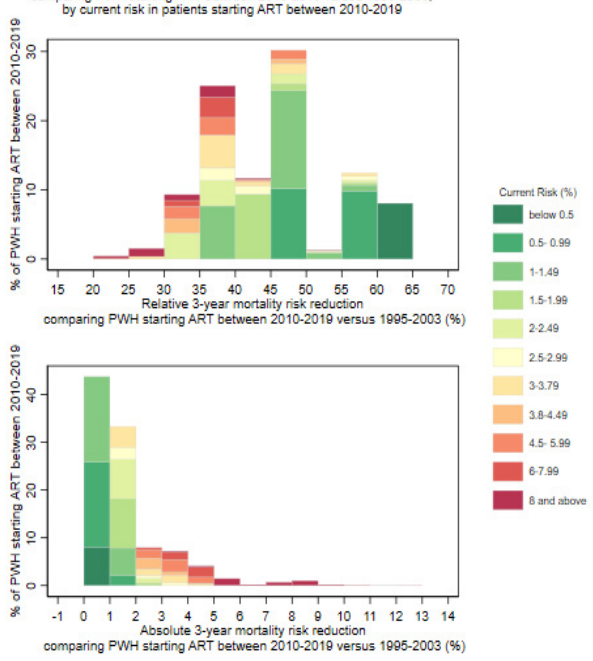
**Background:** Prognosis for mortality among people with HIV (PWH) is important to guide clinical decision making and preventive care. In 2007 we reported prognostic models estimating 3- and 5-year mortality risk for PWH who started ART between 1995 and 2003, but these are unlikely to be calibrated to the modern treatment era. They included CD4 count, HIV viral load, transmission risk group, CDC disease stage, age and sex: prognostic accuracy may be improved by considering additional risk factors.

**Methods:** We analysed data on PWH starting ART between 2010 and 2019 from 20 European and North American cohorts (Antiretroviral Therapy Cohort Collaboration). Flexible parametric survival models were used to estimate mortality risk from ART start and from 6 months after ART start. We calculated both relative risk reduction (RRR) and absolute risk reduction (ARR) for each combination of covariates and compared these between PWH starting ART between 1995-2003 with those starting between 2010-19. We considered additional covariates previously included in the VACS Index: haemoglobin, FIB4, EGFR, albumin, white blood count, BMI and HCV status. We evaluated models' discrimination using C-statistics.

**Results:** Among 85,995 PWH starting ART between 2010 and 2019, 2517 died. The original (2007) ART-CC prognostic model had excellent discrimination (C-statistics 0.79) for predicting mortality among PWH starting ART after 2010. Using the 2007 model, the 3- and 5- year mortality risk for PWH starting ART after 2010 was substantially lower: RRRs were between 20% and 65% and ARRs between 1% and 13%. PWH starting ART after 2010 in high-risk groups (3-year mortality risk ≥6%) had high ARRs but low RRRs (Figure). The additional VACS Index covariates improved the C-statistics for the updated (2021) models to 0.82 at ART start and 0.83 at 6 months. Associations with haemoglobin were weak at ART start but stronger at 6 months.

**Conclusion:** Reductions in mortality risk among PWH treated with ART since its widespread introduction in 1996 are attributable both to risk profiles having improved over time (through earlier diagnosis and treatment), and to lower mortality among people with the same risk profile. Inclusion of additional risk factors improved discrimination of the 2021 ART-CC models, which are useful in predicting mortality risk up to 5 years after ART start in high-income countries in the current treatment era.

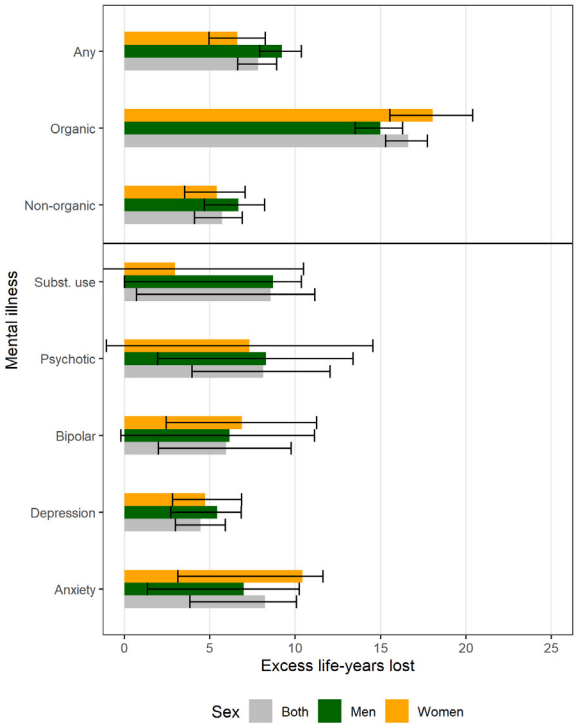
Figure. Distributions of estimated 3-year relative and absolute mortality risk reduction from the original (2007) ART-CC model, comparing PWH starting ART between 2010-2019 versus 1995-2003, by current risk in patients starting ART between 2010-2019



## 766 EXCESS LIFE-YEARS LOST ASSOCIATED WITH HOSPITALIZATION FOR MENTAL ILLNESS

**Yann Ruffieux**[1], Mpho Tlali[2], Anja E. Wettstein[1], Gary Maartens[3], John Joska[3], Morna Cornell[2], Leigh Johnson[2], Nicky Maxwell[2], Veronika W. Skrivankova[1], Mary-Ann Davies[2], Matthias Egger[1], Andreas D. Haas[1]
*[1]Institute of Social and Preventive Medicine, Bern, Switzerland, [2]Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa, [3]University of Cape Town, Cape Town, South Africa*

**Background:** Mental illness can adversely affect HIV treatment outcomes and survival. We estimated excess life-years lost (ELYL) associated with mental illness among people living with HIV in South Africa.
**Methods:** We conducted a cohort study using routine data from the private Aid for AIDS (AfA) disease management program covering the years 2012 to 2018. The cohort was supplemented with mortality records from the South African National Population Register. We followed up patients aged 15 years or older, starting from their date of enrolment into the program until their transfer out, their death, or database closure. We used hospital discharge summaries (ICD-10 diagnoses F00-F99) as indicator of mental illness. We calculated ELYL associated with mental illness by estimating how many more years of life someone with a mental illness was expected to lose before the age of 75 compared to someone without the illness. We divided ELYL into natural and unnatural death components. Additionally, we computed ELYL associated with the following subtypes of mental illnesses: organic disorder (ICD-10 F00-F09), non-organic disorder (F10-F99), psychotic disorder (F20-F29), bipolar disorder (F31), depression (F32, F33, F34.1, F54), and anxiety (F40-F49).
**Results:** Of the 122,853 AfA participants eligible for this study, 8,505 were hospitalized for a mental illness, including 7,102 for depression, 1,133 for anxiety disorder, 1,030 for a substance use disorder, 857 for a bipolar disorder, 545 for an organic disorder and 291 for a psychotic disorder. The mortality rate was 1.9/100 person-years (py) (95% CI 1.7-2.1) in patients with a mental illness and 0.8/100 py (95% CI 0.8-0.9) in patients without. The number of ELYL associated with any mental illness was 7.8 (95% CI 6.7-8.9, Figure), divided into 7.5 (95% CI 6.2-8.5) from natural deaths and 0.4 (95% CI 0.0-0.9) from unnatural deaths. The ELYL were higher in men (9.2, 95% CI 7.9-10.4) than in women (6.6, 95% CI 5.0-8.3). The ELYL associated with organic disorders (16.6, 95% CI 15.3-17.7) were three times that associated with non-organic disorders (5.7, 95% CI 4.1-6.9).
**Conclusion:** Data on life-years lost associated with mental illness in people living with HIV are lacking. We found that, on average, AfA particpants hospitalized for a mental illness lost eight more years of life before the age of 75 compared to the rest of the cohort. Further studies are required that explore the causal pathways between mental illness and mortality in people living with HIV.




## 767 PLASMA RENALASE AND ALL-CAUSE MORTALITY IN PEOPLE WITH AND WITHOUT HIV

**John Chang**[1], Kaku So-Armah[2], Xiaojia Guo[1], Amy Justice[3], Gary Desir[1]
*[1]VA Connecticut Healthcare System, West Haven, CT, USA, [2]Boston University School of Medicine, Boston, MA, USA, [3]Yale University, New Haven, CT, USA*

**Background:** Renalase is a recently discovered flavoprotein that can act as a pro-survival signal in cells. Increased levels of renalase in tissue and plasma have been associated with advanced tumor characteristics and increased mortality in patients with pancreatic cancers. Our objective was to examine plasma renalase and determine its association with mortality by HIV status.
**Methods:** We measured plasma renalase levels from participants in the Veterans Aging Cohort Study (VACS) Biomarker Cohort. Plasma samples were pretreated with acid to expose an epitope of renalase that has pro-growth properties. Renalase levels were measured using enzyme-linked immunosorbent assay (ELISA). We performed a cross-sectional comparison of renalase by HIV status and HIV-1 RNA level using robust linear regression models. In Cox models, renalase levels were divided into quintiles with the lowest quintile used as reference. Both models were adjusted for age, renal function, hemoglobin, diabetes, liver fibrosis, hepatitis C, alcohol use, cardiovascular disease, lipids and soluble CD14.
**Results:** Of 2361 VACS Biomarker Cohort participants, 1532 had HIV, mean (SD) age was 52 (9) years, 2/3 were Black and 5% were female. Median (interquartile ranges) plasma renalase was 9307 (6756, 12238) ng/ml among people with HIV and 8716 (6198, 11879) ng/ml among those without HIV. In adjusted linear regression models, we did not detect a significant association of renalase and HIV status. There was a stepwise increase in renalase with HIV-1 RNA (Figure). In adjusted Cox regression models, we observed that the association of renalase and mortality differed by HIV status (interaction p-value 0.08). The highest quintile (vs. lowest quintile) of renalase was associated with an increased risk of all-cause mortality in people with HIV (adjusted hazard ratio 1.70; 95% CI 1.18 - 2.27). The lower quintiles (vs. lowest quintile) of renalase in people with HIV was not associated with an increased mortality. Similarly, no significant association was found between renalase and mortality in people without HIV.
**Conclusion:** Plasma renalase was significantly associated with HIV viremia and higher all-cause mortality among people with HIV. These novel findings support further investigation of the role of renalase in HIV viral suppression and mortality.

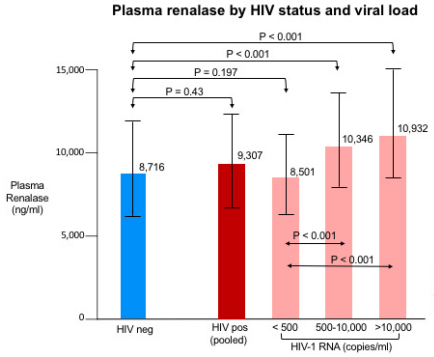



Figure. Results from robust linear regression models adjusting for covariates. Median (with interquartile ranges) of renalase levels are shown.

## 768 CARE AND VIRAL SUPPRESSION AFTER HIV DIAGNOSIS IN US METROPOLITAN AREAS: 2019

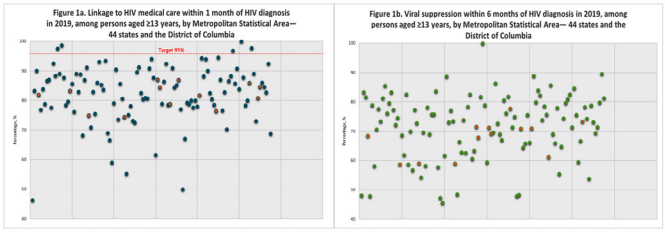
**Shacara Johnson Lyons**[1], Anna Satcher Johnson[1], Jianmin Li[1]
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** In the United States, HIV is concentrated in large metropolitan areas with distinct epidemiological and structural characteristics resulting in varying access to HIV care and treatment. Linkage to HIV medical care and viral suppression are key indicators for monitoring HIV prevention and care programs, however, data for large metropolitan areas (MSAs) are not routinely presented. Identifying gaps in HIV care and treatment can inform programs aimed at reducing HIV transmission.
**Methods:** National HIV Surveillance System data were used to determine care outcomes for persons aged ≥13 years by population density of area of residence and 115 large metropolitan statistical areas (MSAs, population ≥500,000) located within jurisdictions (44 states and the District of Columbia) with complete reporting of CD4 and viral load (VL) results. Percentages linked to HIV medical care (≥1 CD4 or VL result) within 1 month of diagnosis and with

viral suppression (VL <200) within 6 months of diagnosis were determined for persons with HIV diagnosed in 2019.

**Results:** In 2019, overall, 81.3% of persons were linked to HIV medical care within 1 month of diagnosis; 81.8% in 115 large MSAs, 80.2% in small to medium metropolitan areas (50,000-499,999), and 80.1% in nonmetropolitan (<50,000) areas. In large MSAs, linkage ranged from 46.3% (Akron, OH) to 100% (Spokane - Spokane Valley, WA) (median: 83.3%), with ≥95% linkage in five areas (Figure 1a). In MSAs with more than 500 diagnoses, the percentage linked to care varied from 74.4% (Houston-The Woodlands-Sugarland, TX) to 87.0% (Fort Lauderdale-Pompano Beach-Sunrise, FL). In 2019, overall, 68.3% of persons had viral suppression within 6 months of diagnosis; 69.0% in large MSAs, 64.3% in small to medium metropolitan areas, and 67.5 in nonmetropolitan areas. In large MSAs, viral suppression percentages ranged from 45.5% (Fayetteville-Springdale-Rogers, AR) to 100% (Madison, WI) (median: 73.0%; Figure 1b). In MSAs with more than 500 diagnoses, the percentage with viral suppression varied from 58.6% (Chicago-Naperville-Evanston, IL) to 77.7% (New York-Jersey City-White Plains, NY-NJ; New Jersey excluded).

**Conclusion:** Many areas require significant progress to meet the 95% goals set forth for linkage to care and viral suppression in the Ending the HIV Epidemic in the U.S. initiative and HIV National Strategic Plan. Improving HIV care outcomes with early diagnosis and rapid linkage to care and treatment are critical to meet national prevention goals.




*Note. Data are based on residence at diagnosis. Linkage to care was measured by documentation of ≥1 CD4 or VL tests within 1 month of HIV diagnosis in 2019. VL test <200 copies/mL at any time within 6 months of an HIV diagnosis in 2019. Dots represent 115 MSAs within 44 states and the District of Columbia with complete reporting of CD4 and viral load results to the National HIV Surveillance System. Data were excluded for persons residing in states without complete laboratory reporting within the cross-jurisdictional MSA. Orange dots represent MSAs with >500 diagnoses. Please note the y-axis does not start at 0.

## 769 HIV CARE OUTCOMES AMONG FOREIGN-BORN PERSONS WITH DIAGNOSED HIV INFECTION: 2019

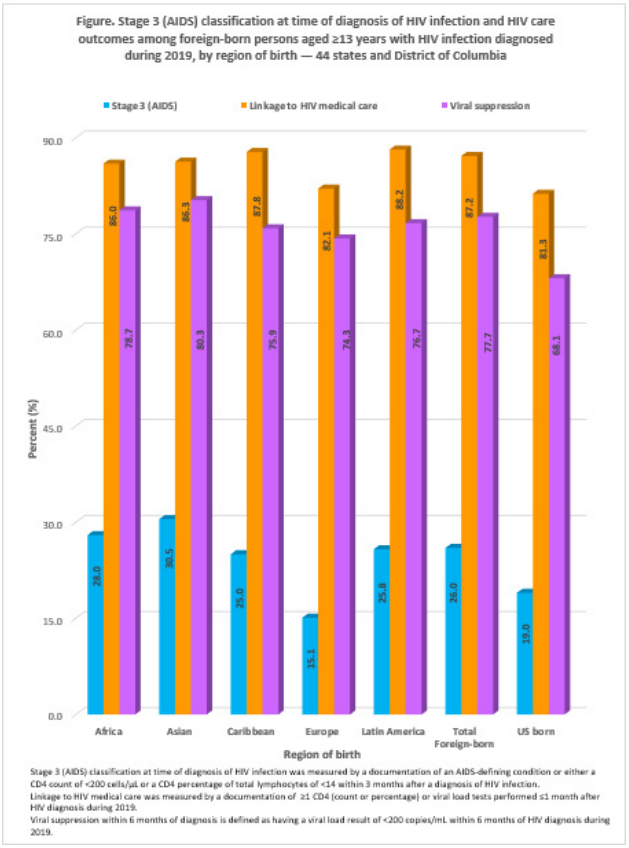
**Tebitha Mawokomatanda**[1], Sonia Singh[1], Eduardo Valverde[1]
[1]*Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** In 2010, foreign-born (FB) persons accounted for 13% of the US population and 16% of new HIV diagnoses. Monitoring HIV diagnoses by region of birth (RoB) may assist in identifying culturally sensitive approaches to improve and optimize care outcomes.

**Methods:** We used NHSS data among persons aged ≥13 years with an HIV diagnosis during 2019 and reported to CDC by December 2020 in 45 US areas. We compared the percentage of HIV stage 3 (AIDS) at time of diagnosis, percentage of linkage to medical care within 1 month of diagnosis, and viral suppression (VS) within 6 months of diagnosis in 2019 among FB persons. We stratified data by RoB, sex at birth, race/ethnicity, age at diagnosis and transmission category. We defined FB persons as anyone who was born outside the US and US territories. HIV stage 3 (AIDS) at time of diagnosis was measured by a documentation of an AIDS-defining condition or either a CD4 count of <200 cells/μL or a CD4 percent of total lymphocytes of <14 within 3 months after a diagnosis of HIV infection. Linkage to care was determined by a documentation of ≥1 CD4 (count or percent) or viral load (VL) tests performed ≤1 month after HIV diagnosis. VS was determined by a VL result of <200 copies/mL at any VL test within 6 months of an HIV diagnosis.

**Results:** Among 5,036 FB persons with an HIV diagnosis during 2019; 47.9% were born in Latin America, 22.1% Caribbean, 18.2% Africa, 8.3% Asia, and 3.5% Europe. Overall, 26.0% of FB persons with an HIV diagnosis were stage 3 (AIDS) compared to 19.0% of US-born. Asian-born (30.5%) persons had the highest proportion of stage 3 (AIDS) diagnosis, while European-born (15.1%) had the lowest. Overall, 87.2% of FB were linked to care compared to 81.3% of US-born. The highest percentage of persons linked to care were from Latin America (88.2%) and the lowest were European born (82.1%). Overall, 81.3% of FB achieved VS compared to 68.1% of US-born. Asian-born (80.3%) had the highest percentage of VS while European-born (74.3%) had the lowest.

**Conclusion: Care** outcomes varied by RoB and selected characteristics. Overall, FB persons have better outcomes than US-born in linkage to care and VS, but more likely to be HIV stage 3 (AIDS). Culturally sensitive HIV testing campaigns should be developed to make sure that FB persons with an HIV diagnosis are diagnosed early to prevent poor clinical outcomes and further spreading the virus.




## 770 DECLINE IN CD4+ COUNTS AND RISK OF SEVERE MORBIDITY IN PLHIV AFTER INITIATING cART

New Investigator Scholar

**Maria Choufany**[1], Laurence Weiss[2], Alain Makinson[3], Hélène Roul[1], Jean-Michel Livrozet[4], Valérie Pourcher[5], Giovanna Melica[6], Christophe Rioux[2], Jean-Paul Viard[2], Esaïe Marshall[1], Sophie Grabar[7], Dominique Costagliola[1]
[1]*Sorbonne University, National Institute of Health and Medical Research (INSERM), Institut Pierre Louis d'Épidémiologie et de Santé Publique (IPLESP), Paris, France,* [2]*Clinical Immunology Department, Hôtel Dieu Hospital, Paris, France,* [3]*University Hospital Montpellier, INSERM U1175, Montpellier, France,* [4]*Department of Infectious and Tropical Diseases, Edouard Herriot Hospital, Lyon, France,* [5]*Infectious and Tropical Diseases Department, Pitié-Salpêtrière University Hospital, Paris, France,* [6]*Infectious Diseases Department, Hospital Group Henri-Mondor/Albert-Chenevier, Créteil, France,* [7]*Sorbonne University, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique (IPLESP), Department of Public Health Saint Antoine Hospital, Paris, France*

**Background:** A previous study showed that a major decline in CD4 counts in persons living with HIV (PLHIV) with suppressed viral load under combined antiretroviral therapy (cART) was associated with an increased risk of severe morbidity and death. Our objectives were to assess the risk of a major CD4 decline, to determine the associated factors, and to evaluate its association with the risk of severe morbidity (cardiovascular disease, cancer, death) in PLHIV who initiated cART between 2006 and 2018.

**Methods:** From the ANRS CO4-FHDH (French Hospital Database on HIV), we considered PLHIV, older than 18 years, followed for at least two years after reaching virologic suppression after cART initiation, with at least 9 months of virologic suppression and without prior cancer or cardiovascular events. A major CD4 decline was defined as 2 consecutive relative differences greater than 15%, computed from moving averages of 3 consecutive CD4 counts. In participants with a major CD4 decline, we modeled CD4, CD8, and total lymphocyte counts before and after the beginning of the CD4 decline by using spline regression. We calculated the incidence rate (IR) of a major CD4 decline, assessed associated factors, and evaluated its association with the risk of severe morbidity, during or after 6 months of the decline by using Poisson regression.

**Results:** Among 14 140 eligible participants (50 372 person-years (PY)), 122 had a major CD4 decline (IR 2.43 per 1000 PY [95% Confidence Interval (CI), [2.07-2.79]). The risk of a major CD4 decline was associated with increasing age (IR ratio, 5.0 [95% CI, 1.5-15.9] in those >50 years vs <30 years of age). Such a decline was also observed for the CD8 and total lymphocyte counts. The adjusted incidence rate of severe morbidity was 5.0 [95% CI, 4.0-6.2]/1000PY for persons with no decline, compared with 73.4 [95% CI, 32.1-168.6] during the first 6 months following the decline and 8.9 [95% CI, 3.3-24.1] after 6 months in persons with a decline. Thus, the risk of severe morbidity was 15-fold higher during the first 6 months for persons who had a CD4 decline versus those with no decline (IR ratio, 14.7[95% CI, 6.6-33.1]). The risk of each event separately was also assessed (see Table).

**Conclusion:** In PLHIV with viral suppression after initiating cART between 2006 and 2018, a major CD4 decline was a rare event and related to global lymphopenia. This decline was associated with age and a higher risk of severe morbidities or death during the first 6 months after the decline.

*Table: Risk of severe morbidity and death before and after CD4 Decline (Yes <6 months: in the first 6 months after the decline; Yes ≥ 6 months: after the first 6 months after the decline)*

| | CD4 Decline | Nb events | PY | IR/1000 PY (CI 95 %) | | IRR (CI 95 %) | |
|---|---|---|---|---|---|---|---|
| | | | | Non-adjusted | Adjusted | Non-adjusted | Adjusted |
| Cardiovascular events | No | 105 | 53680 | 2.0 (1.6-2.4) | 1.2 (0.8-1.8) | | |
| | Yes < 6 months | 1 | 55 | 18.0 (2.6-129.8) | 8.2 (1.1-60.7) | 9.4 (1.3-67.0) | **6.8 (1.0-49.1)** |
| | Yes ≥ 6 months | 0 | 335 | | | | |
| Cancer | No | 208 | 53562 | 3.9 (3.4-4.4) | 2.1 (1.6-2.9) | | |
| | Yes < 6 months | 4 | 47 | 84.3 (31.6-224.6) | 39.0 (14.0-108.9) | 21.7 (8.1-58.4) | **18.0 (6.6-48.5)** |
| | Yes ≥ 6 months | 3 | 310 | 9.6 (3.1-30) | 5.2 (1.6-16.8) | 2.5 (0.8-7.8) | **2.4 (0.7-7.6)** |
| Death | No | 63 | 53268 | 1.2 (0.9-1.5) | 1.0 (0.6-1.6) | | |
| | Yes < 6 months | 2 | 47 | 42.5 (10.6-170.1) | 27.9 (6.4-120.3) | 36.0 (8.8-147.0) | **28.0 (6.8-115.6)** |
| | Yes ≥ 6 months | 1 | 307 | 3.3 (0.5-23.1) | 2.2 (0.3-16.3) | 2.8 (0.4-19.9) | **2.2 (0.3-16.0)** |

## 771 EFFECT OF AIDS DRUG ASSISTANCE PROGRAM VARIABILITY ON TIMELY ART & VIRAL SUPPRESSION

**Julia Thome**[1], David B. Hanna[2], Angela Parcesepe[3], Keri N. Althoff[4], Jonathan A. Colasanti[5], Heidi Crane[6], Audrey L. French[7], Stephen Gange[4], Kelly Gebo[4], Nancy A. Hessol[8], Michael A. Horberg[9], Richard Moore[4], Michael J. Silverberg[10], Peter F. Rebeiro[1]

*[1]Vanderbilt University, Nashville, TN, USA, [2]Albert Einstein College of Medicine, Bronx, NY, USA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]The Johns Hopkins University, Baltimore, MD, USA, [5]Emory University, Atlanta, GA, USA, [6]University of Washington, Seattle, WA, USA, [7]Rush University Medical Center, Chicago, IL, USA, [8]University of California San Francisco, San Francisco, CA, USA, [9]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [10]Kaiser Permanente Northern California, Oakland, CA, USA*

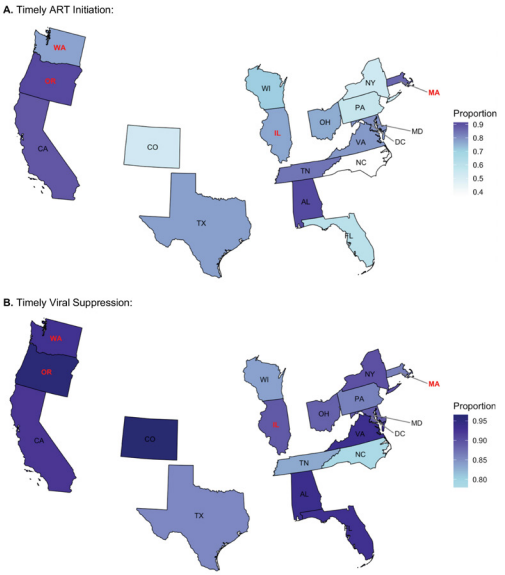
**Background:** AIDS Drug Assistance Programs (ADAPs) are publicly-funded resources for low-income, under- and un-insured people with HIV (PWH) in the US. ADAP formulary openness varies by state, but clinical consequences of cost-saving restricted formularies due to poorer medication availability or related structural factors are unclear. We therefore assessed associations between ADAP formulary openness and timely antiretroviral therapy (ART) initiation and viral suppression (VS) among PWH in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

**Methods:** Using the National Alliance of State and Territorial AIDS Directors' annual ADAP reports, we classified adult (≥18 years old) PWH enrolling at NA-ACCORD clinical sites from 2014-2017 as residing in 'open' states if their ADAP formularies included all FDA-approved medications and 'restricted' otherwise. Individual-level data were used to define outcomes: (1) timely ART initiation was receipt of potent ART with ≥3 agents within 6 months of cohort enrollment; (2) timely VS was an HIV-1 RNA <200 copies/mL within one year of ART initiation. Multivariable modified Poisson regression, with robust variance accounting for clustering by state, yielded adjusted risk ratios (aRR) and 95% confidence intervals for each outcome by ADAP formulary status in states with ≥25 enrolled PWH. Models adjusted for baseline age, birth sex, race/ethnicity, history of injection drug use, CD4 count, state Medicaid expansion status, state median income, census region, and calendar year.

**Results:** Among 14,415 PWH eligible for ART initiation across 18 states, 702 (4.9%) resided in 4 states with open formularies from 2014-2017; among 12,341 PWH eligible for timely VS across 18 states, 672 (5.4%) resided in 4 states with open formularies (Figure). While the % with timely ART initiation was higher (87% vs. 79%) in open vs. restricted formulary states, VS was slightly lower (86% vs. 90%). After adjustment, PWH in states with open formularies had a significantly higher probability of ART initiation (aRR=1.36, 1.19-1.56) and a non-significantly higher probability of VS (aRR=1.02, 0.99-1.05).

**Conclusion:** In this cohort of PWH, ART initiation outcomes were better in states with open ADAP formularies compared to those with restricted formularies, though VS outcomes were not. Longer follow-up and additional study will be required to more precisely quantify the benefits of open state ADAP formularies for successfully linked PWH.

**Figure.** Geographic distribution of people with HIV enrolling in clinical care within the NA-ACCORD from 2014-2017 and the proportion achieving outcomes of timely ART initiation (starting combination ART within 6 months after enrollment) [panel **A**] and timely viral suppression (HIV-1 RNA <200 copies/mL within one year after ART initiation) [panel **B**], by state ADAP formulary status ("open" formulary states are labeled in red font).




## 772 THE IMPACT OF CHURN ON HIV OUTCOMES IN A SOUTHERN UNITED STATES CLINICAL COHORT

**Srinivasa Nithin Gopalsamy**[1], Vincent Marconi[2], Wendy S. Armstrong[1], Jonathan A. Colasanti[1]

*[1]Emory University, Atlanta, GA, USA, [2]Atlanta VA Medical Center, Decatur, GA, USA*

**Background:** With effective HIV treatment, retention in care and adherence to therapy are essential to achieving and maintaining viral suppression (VS), which improves clinical outcomes and reduces transmission. Persons with HIV (PWH) may experience a cycle of engaging and disengaging in care called "churn." While HIV churn is predicted to be more prevalent in the southern United States and has potential to impede the region's Ending the Epidemic goals, it has not been extensively studied with limited data on associated clinical outcomes. We sought to describe churn and its associated outcomes in a large southern clinical cohort.

**Methods:** We conducted a retrospective cohort study involving patients newly establishing care at a Ryan White HIV/AIDS Program-funded HIV clinic in Atlanta, Georgia from 2012 to 2017 with follow-up data collected through 2019. Among 8115 patient receiving care during that timeframe, we identified 1305 PWH who newly established care. The primary exposure was experiencing churn, defined as having a ≥12-month gap between routine clinic visits or viral load (VL) measurements. Outcomes included rate of VS before and after churn, time from first visit to VS, proportion of all collected VL measurements since first visit that are transmissible (≥1500 copies), and cumulative burden of AIDS-defining illness (ADI) per person.

**Results:** Of the PWH newly establishing care, 81.7% were male, 84.9% Black, 43.4% with alcohol use, 28.0% with drug use, and 201 (15.4%) who experienced churn. Prior to churn, 62.7% of the most recent VL measurements were suppressed, but only 35.3% suppressed with first VL on return to care (p-value <0.0001). For the 40 PWH experiencing churn prior to attaining VS, the time from first visit to VS was greater (adjusted HR 0.26, 95% CI 0.18 – 0.38) compared to all other patients, excluding those with VS prior to first visit. Overall, the churn cohort had 30.9% of VL measurements in the transmissible range, compared to 13.7% in the cohort retained in care (p-value <0.0001). There were no increased adjusted odds of ADI in the churn group compared to the retained group (0.63, 95% CI 0.36, 1.11).

**Conclusion:** While churn may not be associated with increased ADI burden, suggesting benefit to having at least some exposure to treatment, it is

associated with delayed VS and decreased rate of VS. Moreover, patients experiencing churn spend more time with transmissible viremia; thus, identifying and mitigating churn may help reduce HIV transmission in the community.

## 773 CHARACTERIZING GEOSPATIAL MOBILITY AMONG PLWH IN TENNESSEE AND ITS IMPACT ON HIV CARE

**Aima A. Ahonkhai**[1], Aihua Bian[1], Natalie Robbins[2], Laurie Maurer[3], Kate Clouse[2], Leslie Pierce[1], Jessica M. Perkins[2], Steven A. Wernke[2], Bryan Shepherd[1], Meredith R. Brantley[3]

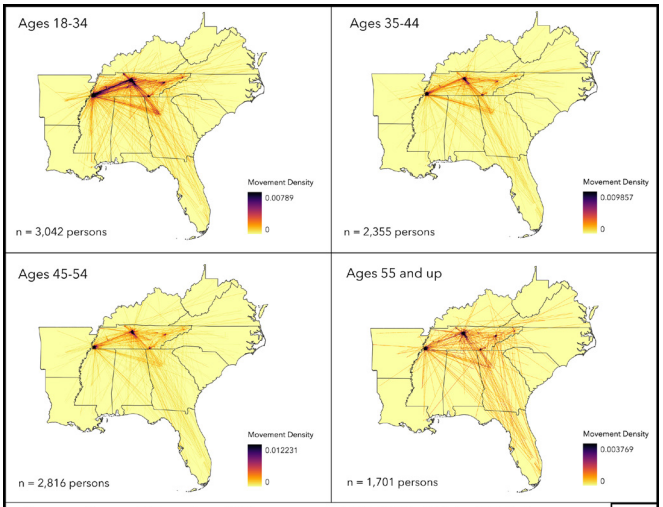
*[1]Vanderbilt University Medical Center, Nashville, TN, USA, [2]Vanderbilt University, Nashville, TN, USA, [3]Tennessee Department of Health, Nashville, TN, USA*

**Background:** Mobility can disrupt engagement in HIV care and may undermine treatment goals. Few datasets on mobility patterns exist, however, and little is known about mobility as a driver of health outcomes among people living with HIV (PLWH) in the US overall, or in the Southern US, which is disproportionately burdened by HIV.

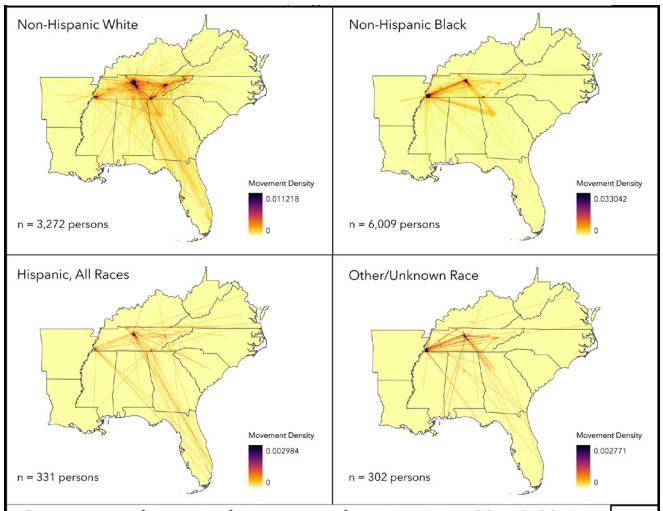
**Methods:** We combined residential Census tract with clinical surveillance data from PLWH in Tennessee from 2016 and 2017. Mobility was assessed as a change in address or via total miles moved. Retention was defined by having two CD4 or HIV RNA lab values in the calendar year at least 3 months apart, whereas loss to follow-up (LTFU) was defined by having a CD4 or HIV RNA lab value in the calendar year, but not meeting the threshold for retention. Viral suppression was defined as having an HIV RNA value <200 copies/mL. To visualize mobility patterns, we applied a kernel density estimator to origin-destination lines representing changes in address, and stratified these transit density visualizations by demographic subgroup. We estimated the association between mobility and HIV care outcomes in the subsequent year using multivariable Poisson regression models.

**Results:** Among 17428 PLWH (mean age of 44 years [SD=12]), 6564 PLWH (38%) had >1 address change and had moved 79 total miles on average (SD=346). We observed in-state movement corridors between four major cities (Chattanooga, Knoxville, Memphis and Nashville) and out-of-state movement corridors between Tennessee and Atlanta, Georgia and between Tennessee and Florida. Homogenous movement patterns within these corridors existed for some subgroups with more heterogenous movement patterns among others [Figure 1]. Having >1 address change (vs. none) was associated with a decreased likelihood of retention (adjusted relative risk [aRR]=0.95; 95%CI 0.93-0.98), and with an increased risk of LTFU (aRR=1.18; 95%CI 1.09-1.27). Greater total miles moved exhibited a dose-response relationship with the risk of retention (aRR=0.53; 95%CI 0.49-0.58) and LTFU (aRR=2.52; 95%CI 2.25-2.83), comparing PLWH who moved 1000 miles vs. 0 miles. There was no association between mobility and viral suppression.

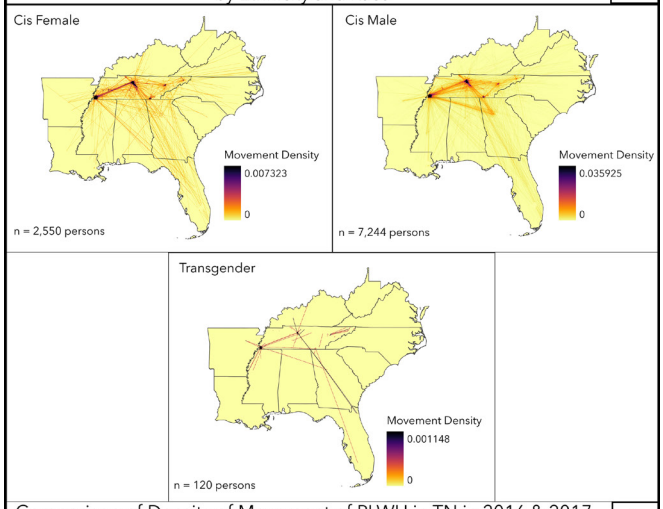
**Conclusion:** Mobility is common among PLWH in Tennessee and is associated with poor engagement in HIV care. Geospatial analyses can help identify movement patterns of highly mobile groups to inform novel interventions to improve continuum of care outcomes.



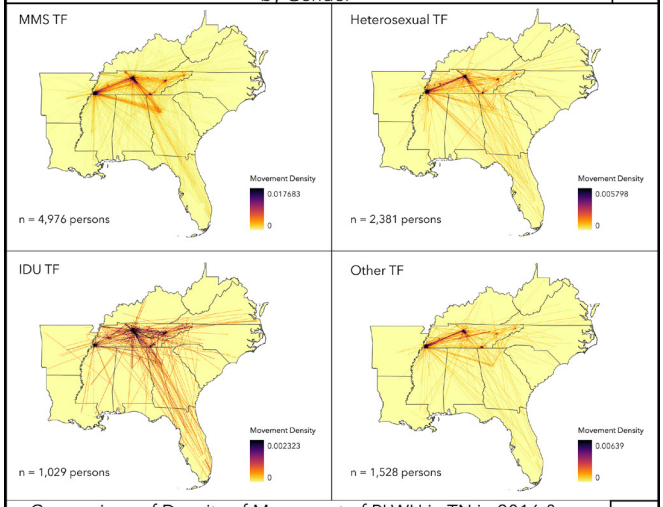

Comparison of Density of Movement of PLWH in TN in 2016 & 2017, by Age — A




Comparison of Density of Movement of PLWH in TN in 2016 & 2017, by Ethnicity and Race — B




Comparison of Density of Movement of PLWH in TN in 2016 & 2017, by Gender — C




Comparison of Density of Movement of PLWH in TN in 2016 & 2017, by Transmission Factor — D

## 774 LATINOS WITH HIV IN DC: AN INTERSECTIONAL APPROACH EXPLORING HIV HEALTH OUTCOMES

**Leah Varga**[1], Morgan Byrne[2], Marinella Temprosa[2], Michael A. Horberg[3], Carlos Rodriguez-Diaz[2], Anne Monroe[2], Amanda Castel[2]

*[1]District of Columbia Department of Health, Washington, DC, USA, [2]George Washington University, Washington, DC, USA, [3]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA*

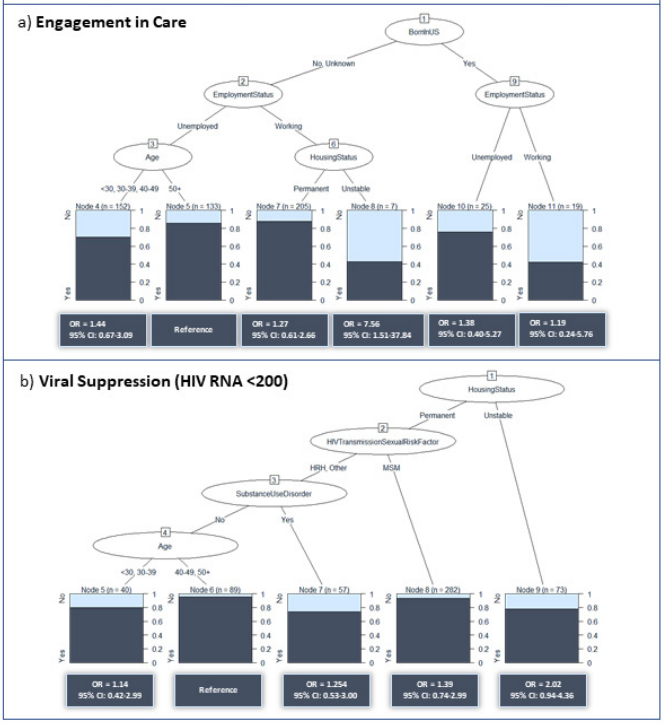
**Background:** Latina/o/xs (Latinos) are disproportionately affected by HIV, and multiple intersectional positions may affect their health outcomes. Using an intersectional approach, we explored engagement in care and viral suppression among adult Latinos enrolled between 2011-2019 in the DC Cohort, a longitudinal EHR-based cohort of PWH at 15 clinics in Washington, DC.

**Methods:** We analyzed socio-structural factors for associations with engagement in care (two visits at least 90 days apart in the past 12 months and lab work in the past 12 months) and viral suppression (< 200c/mL). Variables included: age, gender identity, HIV risk category, country of birth, mental health diagnosis, substance use, most recent housing, employment, and insurance status. Using an intersectional framework, chi-square statistics assessed bivariate relationships, and Chi-squared Automatic Interaction Detector (CHAID) identified mutually exclusive subgroups associated with the outcomes, without assumptions of additivity. CHAID was used to understand outcomes between groups at each intersection, allowing for observation of each intersection's impact on the outcomes by making predictions for the intersections. Logistic regression was used to quantify the prediction probability of terminal nodes.

**Results:** Of 541 participants, the majority were cisgender male (85%), median age was 47 years, and 48% were foreign-born. Approximately 31% had a substance use disorder, and 49% had been diagnosed with a mental illness. Most participants accessed care through a community site (77%), 86% were stably housed, 43% were employed, and 93% were insured; 80% were engaged in care, and 88% were virally suppressed in the prior 12 months. Results from the CHAID model indicated that foreign-born Latinos, employed, and permanently housed were the most engaged in care (Figure 1). Those least likely to be engaged had the same profile, but unstable housing. Groups most likely to be virally suppressed were permanently housed MSM or permanently housed non-MSM, without substance use disorders, and older than 40 years. Latinos with substance use, non-MSM, and permanently housed had the lowest rate of viral suppression.

**Conclusion:** Using an intersectional framework revealed combinations of mainly structural factors, particularly housing, had the greatest impact on HIV health outcomes among Latinos. Understanding multi-level factors that impact engagement in care and viral suppression can help design appropriate multi-level interventions to reduce inequities.

**Figure.** CHAID decision tree for variables of a)**Engagement in Care** and b)**Viral Suppression** during most recent 12 months of Follow-up, DC Cohort




## 775 EFFECT OF SOCIAL DETERMINANTS OF HEALTH ON UNCONTROLLED HIV INFECTION

**Jason S. Melo**[1], Nancy A. Hessol[2], Sharon Pipkin[1], Ling Hsu[1]
*[1]San Francisco Department of Public Health, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA*

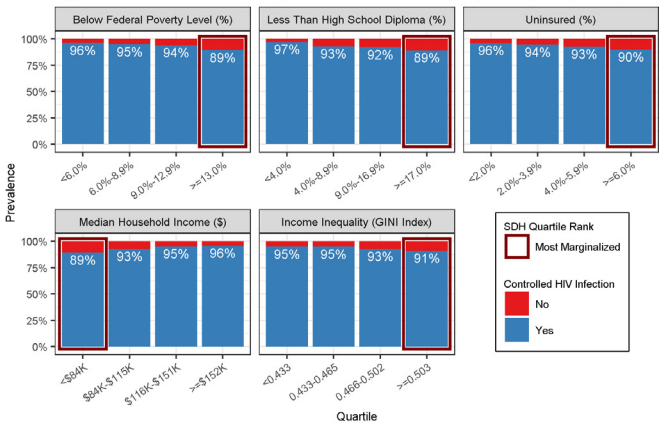
**Background:** In 2013-2014, the San Francisco Department of Public Health (SFDPH) established programs to rapidly link people with HIV (PWH) to care and offer antiretroviral therapy (ART) at HIV diagnosis. Such programs reduced the number of PWH out of care or with detectable HIV viral load (i.e., uncontrolled HIV). Beyond these programs there are social, structural, and environmental factors that contribute to access to HIV care and ART. We investigated the role of social determinants of health (SDH) on uncontrolled HIV among PWH in San Francisco.

**Methods:** Data from PWH ages 18 and older in the SFDPH case registry, who were diagnosed and alive as of 12/31/2019, prescribed ART, and known to be San Francisco residents during 2017-2019 were analyzed in conjunction with SDH metrics derived from the American Community Survey 2015-2019, linked by census tract. We focused on five census tract-level SDH metrics: percent of residents below the federal poverty level, with less than a high school diploma, or uninsured; median household income; and GINI index, an income inequality metric. We compared uncontrolled HIV (viral load >200 copies or viral load and CD4 test absent) prevalence across quartiles of each metric independently, constructing logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI), with the least marginalized quartile (LMQ) as the referent group for each metric (see Figure 1).

**Results:** The cross-sectional analysis included 7188 PWH (6696 controlled HIV; 492 uncontrolled HIV). Most were men (90%), white (54%), 50-59 or 60-69 years old (35% and 26%, respectively), men who have sex with men who do not inject drugs (72%), and USA-born (72%). We observed decreasing prevalence of controlled HIV in increasingly marginalized quartiles across all SDH metrics (Figure 1). Similarly, the unadjusted OR of uncontrolled HIV rose with increasingly marginalized quartiles, compared to the LMQ for each metric. Adjusting for demographics and transmission category, the OR for uncontrolled HIV for PWH in the most marginalized quartile remained significant across metrics for poverty [OR=2.0,CI(1.5,2.6)], education [OR=2.4,CI(1.8,3.2)], insurance [OR=1.8,CI(1.3,2.5)], income [OR=1.8,CI(1.4,2.3)], and income inequality [OR=1.5,CI(1.1,2.0)].

**Conclusion:** Social determinants of health differentially affect the ability of PWH to control HIV. Despite established care programs, PWH experiencing socioeconomic marginalization may require additional support to achieve health outcome goals.

**Figure 1. Prevalence of controlled HIV by social determinant of health (SDH) metric quartile (n=7188)**




## 776 MENTAL HEALTH DISORDERS IN PEOPLE WITH HIV AND THE EFFECTS ON THE HIV CARE CONTINUUM

New Investigator Scholar

**Raynell Lang**[1], Jiafeng Zhu[1], Kristen McArthur[1], Michael A. Horberg[2], David J. Grelotti[3], Kalysha Closson[4], Viviane D. Lima[4], Angela Parcesepe[5], Paul S. Nestadt[6], Reena Camoens[7], Mona Loutfy[8], Judith Cook[9], Joseph Goulet[10], Keri N. Althoff[1]
*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [3]University of California San Diego, San Diego, CA, USA, [4]University of British Columbia, Vancouver, Canada, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]Johns Hopkins School of Medicine, Baltimore, MD, USA, [7]Family Psych Services, PLLC, Nashville,*

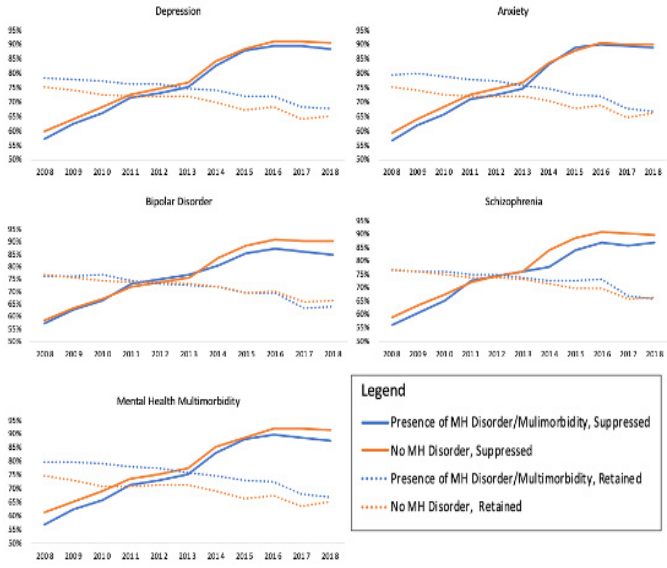
*TN, USA, [8]Women's College Research Institute, Women's College Hospital, University of Toronto & Maple Leaf Medical Clinic, Toronto, Canada, [9]University of Illinois at Chicago, Chicago, IL, USA, [10]Yale School of Medicine & VA Connecticut Healthcare System, West Haven, CT, USA*

**Background:** Mental health (MH) conditions are a significant source of morbidity and mortality globally, with a higher burden in people with HIV (PWH). However, treat-all era differences in HIV outcomes for those with and without MH conditions are understudied, and essential for informing the "Ending the HIV Epidemic" (EHE) initiative. We describe the prevalence of depression, anxiety, bipolar disorder (BD) and schizophrenia in PWH and the differences in HIV care continuum outcomes in those with and without MH conditions.

**Methods:** Using data from adults (≥18 years) with HIV in the NA-ACCORD, we estimated annual prevalence of anxiety disorders, depressive disorders, BD and schizophrenia from 2008-2018 based on ICD code mapping. MH multimorbidity was defined as having 2 or more mental health diagnoses. Log binomial models with generalized estimating equations estimated crude (PR) and adjusted prevalence ratios (aPR) and 95% confidence intervals ([,]) for retention in care (≥2 HIV primary care visits >90 days apart in a calendar year) and HIV viral suppression (HIV RNA <200 copies/mL at last measurement of the year) by presence vs. absence of each MH condition in the most recent calendar years (2016-2018). Covariates in adjusted models included age, race/ethnicity, HIV acquisition risk and cohort.

**Results:** Among 122,896 PWH in HIV care from 2008-2018, 67,643 (55.1%) were diagnosed with 1 or more of four assessed MH diagnoses: 39% with depressive disorders, 28% with anxiety disorders, 10% with BD, and 5% with schizophrenia. The prevalence of depressive and anxiety disorders increased between 2008-2018, while BD and schizophrenia prevalence were stable. MH multimorbidity (vs. no MH diagnoses) was common affecting 24% of PWH. Regardless of MH diagnoses, retention in care decreased over time, however viral suppression increased (Figure 1). From 2016-2018 (N=64,684), retention in care and HIV viral suppression prevalence did not differ by single MH diagnosis, however those with MH multimorbidity (16%) had a greater prevalence of retention in care (PR=1.04 [1.04, 1.05]) but lower prevalence of viral suppression (PR=0.98 [0.97, 0.99]) compared to those without MH diagnoses.

**Conclusion:** The prevalence of MH and MH multimorbidity among PWH was high. Although retention was similar to people without MH diagnoses, viral suppression was lower in those with MH multimorbidity. To achieve EHE goals of viral suppression, tailored interventions for PWH with MH multimorbidity may be needed.




## 777 PATTERNS OF SUBSTANCE USE AND MENTAL HEALTH SYMPTOMS AMONG PEOPLE WITH HIV IN CARE

**Anthony T. Fojo**[1], Catherine R. Lesko[2], Nikki Shen[2], Jarratt D. Pytell[1], Richard Moore[1], Marybeth McCauley[1], Heidi Hutton[1], Edward R. Cachay[3], Heidi Crane[4], Katerina Christopoulos[5], Michael Saag[6], Kenneth H. Mayer[7], Brian W. Pence[8], Geetanjali Chander[1], Bryan Lau[2]

*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]University of California San Diego, San Diego, CA, USA, [4]University of Washington, Seattle, WA, USA, [5]University of California San Francisco, San Francisco, CA, USA, [6]University of Alabama at Birmingham, Birmingham, AL, USA, [7]Harvard Medical School, Boston, MA, USA, [8]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** Mental health symptoms and substance use are prevalent among people with HIV (PWH), and are each associated with poor HIV outcomes. These conditions are intertwined, and likely interact in many ways. Identifying meaningful patterns in how they co-occur is challenging but could have important clinical implications.

**Methods:** We randomly selected 4,000 participants from the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) with two or more visits during which they completed patient-reported measures of depression andpanic symptoms, and reported frequency of alcohol, tobacco, opioids, cocaine, amphetamine, and marijuana use between October 2005 and May 2018. We performed a cluster analysis, using the random forest sidClustering algorithm. For the resulting clusters, we calculated the mean and interquartile range for each of the 9 items representing mental health symptoms and substance use, as well as the proportion who had a viral load ≤200 copies/mL at their next laboratory draw.

**Results:** The 4,000 participants were 83% male, 47% non-Hispanic White, 35% non-Hispanic Black, and 14% Hispanic and contributed 20,474 encounters. Participants reported using tobacco cigarettes at 33% of encounters, marijuana at 28%, binge drinking at 11%, amphetamines at 7%, cocaine at 6%, and opioids at 2%. Participants reported a mean of 1.8 drinks per day, with 37% of encounters showing moderate to severe depression and 25% of encounters reporting any panic symptoms. The clustering algorithms identified four clusters (see Figure). In a cluster with minimal mental health symptoms and little substance use, 88% of PWH were subsequently virally suppressed. Suppression was lower for those with high depression and panic symptoms without much substance use (83%) and those with frequent substance use (largely cocaine and opioids) without mental health symptoms (87%). Suppression was lowest in a cluster with mental health symptoms plus frequent substance use (78%). Differences in viral suppression were significant with $p < 0.001$.

**Conclusion:** Depression and panic symptoms co-occur, both with and without concomitant substance use; a distinct subset of PWH endorse cocaine and opioid use without concomitant depression or panic symptoms. The ways in which mental health symptoms co-occur with substance use are associated with viral non-suppression. Further analysis could identify patterns of mental health symptoms with use of specific substances.

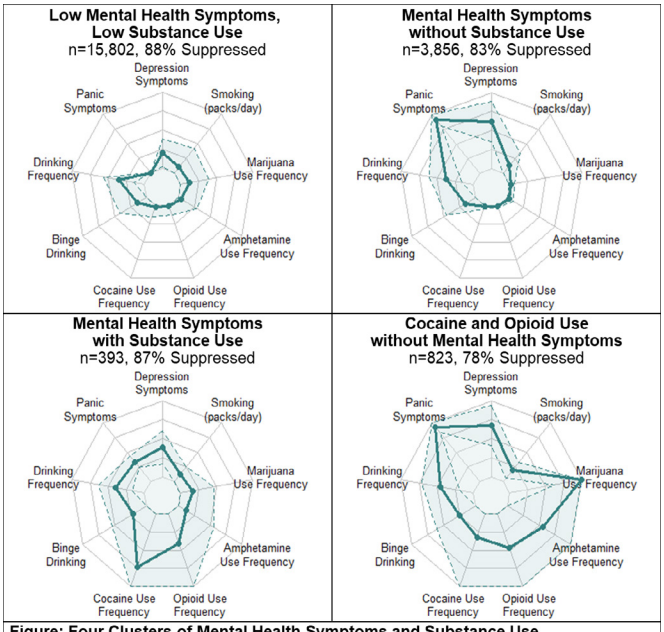



**Figure: Four Clusters of Mental Health Symptoms and Substance Use**
Each of the 6 items is plotted on a normalized scale where each tick from the center represents approximately one standard deviation at the population level. Circles denote the mean for each item; dashed lines denote the interquartile range. Viral suppression = viral load ≤200 copies/mL.

## 778 IMPACT OF METHAMPHETAMINE USE ON VIRAL LOAD BY GENDER AMONG PEOPLE WITH HIV

**Rob J. Fredericksen**[1], Robin M. Nance[1], Lydia N. Drumright[1], Bridget M. Whitney[1], Stephanie A. Ruderman[1], Jimmy Ma[1], Andrew W. Hahn[1], Edward R. Cachay[2], Geetanjali Chander[3], Jeffrey M. Jacobson[4], Kenneth H. Mayer[5], Sonia Napravnik[6], Amanda Willig[7], Heidi Crane[1]
*[1]University of Washington, Seattle, WA, USA, [2]University of California San Diego, San Diego, CA, USA, [3]The Johns Hopkins University, Baltimore, MD, USA, [4]Case Western Reserve University, Cleveland, OH, USA, [5]Fenway Institute, Boston, MA, USA, [6]University of North Carolina, Chapel Hill, NC, USA, [7]University of Alabama, Birmingham, AL, USA*

**Background:** Among people with HIV (PWH), methamphetamine (MA) use is ~10 fold higher than in the general population and some studies suggest large gender differences in MA use. Yet, gender MA use difference has not been well assessed in PWH. We characterized gender differences in MA use and impact on viral load (VL) among PWH in HIV care in a geographically and ethnically diverse multi-site US cohort.
**Methods:** Within the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS), PWH self-administer a patient-reported outcomes (PRO) assessment, including questions regarding substance use, prior to routine care visits. PWH who responded to questions about MA use were included in time-updated linear mixed models examining associations between MA use and VL (log2 transformed, last value carried forward for both measures). Models were adjusted for age, race/ethnicity, and years from the first VL, and were parameterized with a random intercept, a random slope for years from the first VL, and an exchangeable correlation matrix.
**Results:** Among PWH (n=17,521, median age 45, 81% cisgender male, 17% cisgender female, 1% transgender female or male; 96% of transgender PWH were female-identified) 10% had used MA in the past 3 months (12%, 3%, 14%, respectively). Overall, there was an average of 10 observations per person over an average follow-up period of 5 years. Among cisgender men, MA use was associated with a VL 1.77 times higher than non-MA using cisgender men (Table 1). Among cisgender women, MA use was associated with a VL 2.41 times higher than non-MA using cisgender women. However, among transgender PWH, those using MA had a VL 3.94 times higher than non-MA-using transgender persons (p<.001 for all associations). Additionally, among all gender groups, daily MA use had twice the effect on VL compared to PWH who used once or twice in the past 3 months (p<.001, results not shown). Using MA in the past 3 months had a statistically significantly greater impact on VL among cisgender females and transgender persons relative to cisgender males (p=.004 and p<.001), respectively (Table 1).
**Conclusion:** While MA use was high among cisgender men, MA use appears to have a greater impact on cisgender women and transgender persons' HIV VL. Prioritizing engagement and retention of cisgender women and transgender PWH in MA treatment may improve virologic outcomes.

**Table 1. Methamphetamine (MA) use and viral load among people with HIV in care in the U.S.***

| Variable | Coefficient | P-value | 95% CI | |
|---|---|---|---|---|
| | | | | |
| Current MA use | 0.825 | <0.001 | 0.751 | 0.898 |
| | | | | |
| Sex/gender (male reference) | | | | |
| Female | 0.237 | <0.001 | 0.153 | 0.322 |
| Transgender | -0.172 | 0.228 | -0.452 | 0.108 |
| | | | | |
| Interaction of current MA use and gender | | | | |
| Female x MA use | 0.446 | 0.004 | 0.141 | 0.751 |
| Transgender x MA use | 1.152 | <0.001 | 0.552 | 1.753 |
| | | | | |
| Race/eth (White ref) | | | | |
| 1: Black | 0.244 | <0.001 | 0.173 | 0.315 |
| 2: Hispanic | 0.052 | 0.292 | -0.044 | 0.147 |
| 3: Other/missing | 0.076 | 0.326 | -0.076 | 0.228 |
| | | | | |
| Age (per year) | -0.038 | <0.001 | -0.040 | -0.035 |
| Years from first VL | -0.154 | <0.001 | -0.183 | -0.125 |
| Intercept | 7.519 | <0.001 | 7.385 | 7.652 |

*Multivariable linear mixed model with log2 transformed VL as the outcome, including a random intercept and a random slope for years from first VL

## 779 VIRAL SUPPRESSION BY 3 MONTHS OF DIAGNOSIS AS AN INDICATOR OF PROGRESS IN HIV CARE

**Sierra Upton**[1], Irina Tabidze[2], Jeff Lauritsen[2], Mark S. Dworkin[1]
*[1]University of Illinois at Chicago, Chicago, IL, USA, [2]Chicago Department of Public Health, Chicago, IL, USA*

**Background:** Prompt initiation of antiretroviral therapy increases the likelihood of achieving viral suppression, which reduces morbidity, mortality, and HIV transmission risk. The National HIV/AIDS Strategy progress indicators to improve the HIV Care Continuum include increasing viral suppression among people with HIV to 95% by 2025. A 2019 New York study proposed an additional indicator, percentage achieving viral suppression within 3 months of diagnosis, to monitor progress in HIV care among newly diagnosed persons. We examined this metric in Chicago. We hypothesized that the proportion of virally suppressed persons has increased.
**Methods:** HIV surveillance data reported to the Chicago Department of Public Health during 2009-2019 were analyzed. Only newly diagnosed Chicago residents aged ≥13 were included. We determined the cumulative percentage achieving viral suppression (<200 copies/mL) within 3 months of diagnosis and linked to care within 1 month of diagnosis. We performed tests for linear trend and chi-square for differences in suppression by sex, race, age, and transmission risk factor.
**Results:** A total of 9,068 persons aged ≥13 were diagnosed with HIV in Chicago between 2009-2019, of which 8,557 were included in the analysis (83.5% male, 16.5% female, 53.5% NH Black). Viral load results were available for 7,733 and of those 28.9% were suppressed within 3 months of diagnosis. In 2019 (and 2009-2019), NH Black persons were less likely to be suppressed compared to other groups (34.9% and 21.7%, respectively; p<.0001). Relatively lower viral suppression was also observed among females (32.3%) and those ≥45 years (33.1%) (p=0.02). Overall, trends in the proportion of viral suppression within 3 months and linkage to care within 1 month improved (p<.0001). Specifically, 42.9% of persons newly diagnosed in 2019 achieved suppression within 3 months, almost 5 times greater than 2009 (8.7%). Linkage to care within 1 month of diagnosis increased from 67% in 2009 to 80.5% in 2019. All groups experienced improvement in viral suppression during the study period, however injection drug users and persons ≥45 years had the smallest relative increase (2.4-fold and 3.2-fold, respectively).
**Conclusion:** The proportion of viral suppression among newly diagnosed persons has increased. However, we identified important disparities by sex, race, age, and transmission risk. These data demonstrate the potential value of the indicator proposed by the NYC Department of Health. We support a broader adoption of this metric.

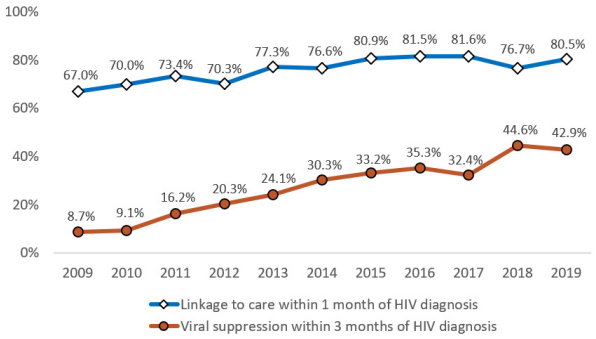



**Figure 1.** Percentages of newly diagnosed persons achieving viral suppression within 3 months and linked to care within 1 month of HIV diagnosis in Chicago, 2009-2019.

## 780 VIRAL SUPPRESSION AMONG PERSONS ENROLLED IN HIV RECENT INFECTION SURVEILLANCE: ZAMBIA

**Zaena Tessema**[1], Elyssa Stoops[2], Aaron Shibemba[3], Lumbani Phiri[4], Simon Agolory[2], Kennedy Nkwemu[2], Samuel Yingst[2], Dailes Nsofwa[2], Leigh Tally[2], Peter Minchella[2], Melissa Arons[1], Canditra McLemore[1], Kemba N. Lee[1]
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]Centers for Disease Control and Prevention, Lusaka, Zambia, [3]Government of Zambia Ministry of Health, Lusaka, Zambia, [4]Center for Infectious Disease Research in Zambia, Lusaka, Zambia*

**Background:** As part of HIV recent infection surveillance in Zambia, baseline viral load (VL) testing and rapid tests for recent infection (RTRIs) are performed on all clients who are newly diagnosed with HIV. A client newly diagnosed with HIV who has a positive rapid test for recent infection (RTRI) was most likely infected with HIV within the past 12 months and is characterized as a recent infection. VL testing reduces misclassification, as a VL <1,000 copies/mL likely indicates viral load suppression (VLS) from current or recent antiretroviral use. We reviewed VLS data among clients in Zambia newly diagnosed with HIV as part of the recent HIV surveillance program.

**Methods:** We analyzed recent infection surveillance data from four provinces in Zambia, from March - August 2021, for newly HIV diagnosed clients ≥ 15 years with a recent or long-term (likely infected with HIV more than 12 months ago) RTRI result and a VL result. Among 11,350 newly HIV diagnosed clients, 8,928 (78.7%) had a VL result. We conducted a descriptive analysis examining proportions of clients with VL suppression (<1,000 copies/mL) by RTRI status, age, sex, province, and modality. Bivariate analysis was conducted with chi-square tests to detect associations between demographic variables and VLS.
**Results:** Among the newly HIV diagnosed clients with a VL result, 3,301 (37.0%) were virally suppressed. The highest proportions of clients virally suppressed were among clients aged ≥30 years (39.9%), females (39.3%), those tested in the Central Province (43.5%), and those diagnosed with HIV as part of index testing services (43.9%). The lowest proportions were clients aged 15-19 years (28.1%), male (33.2%), those tested in Lusaka Province (35%), and those diagnosed by prevention of mother-to-child transmission (PMTCT) programs (24.1%). All demographic variables and VLS were significantly associated (p-value <0.01).
**Conclusion:** Recent HIV infection data from Zambia suggest that a considerable proportion of newly HIV diagnosed clients have previous exposure to antiretroviral therapy (ART)and are likely not true new HIV diagnoses. The proportion virally suppressed varies by geography and demographics, suggesting that these factors may influence which clients choose not to disclose their previous HIV diagnosis. Further study of these relationships using quantitative and qualitative methods may contribute to a better understanding of this behavior and improve screening.

**TABLE 1. Demographic characteristics of viral suppression among persons with new human immunodeficiency virus (HIV) diagnoses at health facilities implementing recent HIV infection surveillance in Zambia, March–August 2021**

| | | N | Number Virally Suppressed (%) | Chi-Square p-value |
|---|---|---|---|---|
| **RTRI Result** | Long-Term | 7,921 | 2,703 (34.1%) | <0.001 |
| | Recent | 1,007 | 598 (59.4%) | |
| **Age** | < 30 years | 3,398 | 1,093 (32.2%) | <0.001 |
| | ≥30 years | 5,472 | 2,182 (39.9%) | |
| **Sex** | Female | 5,438 | 2,138 (39.3%) | <0.001 |
| | Male | 3,404 | 1,129 (33.2%) | |
| **Province** | Central | 635 | 276 (43.5%) | <0.001 |
| | Copperbelt | 2,771 | 1,087 (39.2%) | |
| | Lusaka | 4,905 | 1,716 (35.0%) | |
| | Southern | 617 | 222 (36.0%) | |
| **Modality** | Index | 2,090 | 917 (43.9%) | <0.001 |
| | PITC | 1,550 | 458 (29.5%) | |
| | PMTCT | 818 | 197 (24.1%) | |
| | VCT | 3,013 | 1,152 (38.2%) | |
| | VMMC | 35 | 15 (42.9%) | |

Abbreviations: PITC=provider-initiated testing and counseling; PMTCT=prevention of mother-to-child transmission; VCT=voluntary counseling and testing; VMMC=voluntary medical male circumcision.

## 781 PRIORITIZING HIV-1 TRANSMISSION CLUSTERS FOR INTERVENTION: A PHYLOGENETIC APPROACH

New Investigator Scholar

**Rachel L. Miller**[1], Angela McLaughlin[1], Richard Liang[1], Delphine Duhirwe[1], Anh Le[1], Chanson Brumme[1], Julio S. Montaner[1], Jeffrey B. Joy[1]
*[1]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada*

**Background:** A quantitative framework for prioritizing intervention benefits public health officials needing to address many HIV transmission clusters under time and resource constraints. Using empirical and simulated data, we evaluate the hypothesis that HIV transmission cluster prioritization measures based on phylogenetically-derived lineage-level diversification rates will exceed commonly-used non-phylogenetic prioritization measures in highlighting clusters in urgent need of intervention, without subjectivity or need for supporting data.
**Methods:** 35,752 HIV partial pol sequences collected from 9,822 participants between 1996-2019 were used to infer approximate maximum-likelihood phylogenetic trees rooted by root-to-tip regression. Transmission clusters were inferred using a patristic distance threshold of 0.02 substitutions/site, such that lineage-level diversification rates calculated for all tips could be summarized by cluster. The same methods were applied to simulated epidemic sequence data generated to mimic the BC epidemic using FAVITES.
**Results:** Empirical data suggest diversification-rate based measures perform comparably to non-phylogenetic measures in recreating transmission cluster prioritization choices made by public heath teams (Figure 1). However, analysis of unbiased simulated data reveals a stronger relationship between diversification rate-based measures and future cluster growth, particularly long-term growth (median Spearman r = 0.39 vs 0.17). Diversification rate-based measures also highlighted groups with significantly more future transmissions than random groups of equal size (Mann-Whitney p<0.001). Furthermore, the relationship between diversification rate measures and future growth was notably more robust to decreased sampling proportion.
**Conclusion:** Phylogenetically-derived lineage-level diversification rate-based measures not only frequently outperform non-phylogenetic measures and show less sensitivity to lower sampling, but also offer several additional advantages beneficial to optimization of the public health prioritization process.

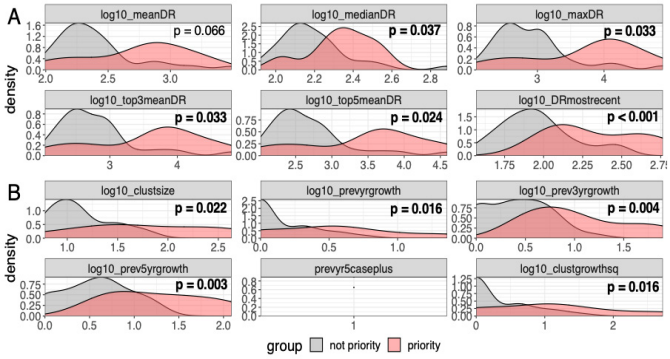



**Figure 1.** Density plots showing the difference in A) phylogenetic diversification rate-based measures or B) non-phylogenetic measures between clusters defined as "priority" by the current public health protocol for immediate intervention and the remainder of the clusters to next be addressed, marked here for the purpose of comparison as "not priority". Only clusters that grew in the past year are shown. Infinite values created by the log10 transformation were forced to 0 for visualization purposes. In panel B, the bottom middle cell shows nothing because in 2018 this binary measure is the same for all clusters, making stratification of cluster values impossible.

## 782 PHYLOGENETIC TRACKING OF HIV EPIDEMIC GROWTH IN QUEBEC FROM 2014 TO 2020

**Bluma G. Brenner**[1], Réjean Thomas[2], Isabelle Hardy[3], Ruxandra-Ilinca Ibanescu[1], Jean-Pierre Routy[4], Michel Roger[5]
*[1]Lady Davis Institute for Medical Research, Montreal, Canada, [2]Clinique Médicale l'Actuel, Montreal, Canada, [3]Centre Hospitalier de l'Université de Montréal, Montreal, Canada, [4]McGill University Health Centre Research Institute, Montreal, Canada, [5]Centre Hospitalier de l'Université de Montreal, Montreal, Canada*

**Background:** Ending the HIV Epidemic by 2030 initiative includes phylogenetics as a molecular framework to track patterns of HIV spread. In this study, phylogenetics was combined with available epidemiological data to elucidate track evolving trends in HIV-1 spread among Men having Sex with Men (MSM) and Heterosexual (HET) populations in Quebec.
**Methods:** Phylogenetic linkage analysis was performed using MEGA-10 and HIV-TRACE/ Microbe-TRACE methodologies. New infections genotyped between 2014—2020 were stratified into groups: i) Subtype B MSM (subtype B male singletons/male-male clusters, n=1812); ii) Subtype B Heterosexual (female singletons/female-male clusters, n=432), including migrants from the Caribbean and Americas; and iii) Non-B subtype (n=737) epidemics. Test requisition data and clinical data from Clinique Actuel (n=141 and 50, 2016-2018) monitored epidemiological features in a subset of newly diagnosed persons.
**Results:** Among MSM, annual new infections declined by 20% and 40% over the 2015-2017 and 2018-2020 periods, respectively. Overall, 45% of new infections in MSM were associated with 20 active large clusters, adding 8—-96 infections/clusters from 2014-2020. Clinical data showed 37% newly diagnosed MSM were born outside Canada, 28% of whom were linked to large cluster outbreaks. Among heterosexuals with subtype B infections, there was a 31% increase from 2015—2017 followed by a 36% decline from 2018-2020 post-COVID. Of note, large cluster HET outbreaks occurred in Quebec City, Richelieu, and Northern Quebec Overall, non-B subtype infections remained steady (median 100 annually) over the 2014 to 2020 period. Several non-B subtype clusters reflect the domestic introduction and spread of subtype CRF02_ AG variants. Cluster membership and cluster size was associated with recent stage infection, viral sequence recency (based on % mixed base calls) and younger age of members within individual clusters.
**Conclusion:** Annual numbers of new HIV-1 infections have steadily declined among MSM post-2008, concomitant to improved HIV prevention paradigms. Epidemic control among MSM and HET groups has been thwarted by large cluster outbreaks. Recent arrivals to Quebec accounted for a growing number of subtype B and non-B subtype infections. HIV prevention efforts must continue

in the post-COVID era, tailored to avert transmission cascades in younger persons and recent migrant populations.

## 783 MOLECULAR ANALYSIS SUGGESTS LOW ONWARD HIV-1 TRANSMISSION AMONG MIGRANTS IN GREECE

New Investigator Scholar

**Evangelia G. Kostaki**[1], Stefanos Limnaios[1], Maria Chini[2], George Adamis[3], Vasileios Papastamopoulos[4], Anastasia Antoniadou[5], Simeon Metallidis[6], Vasileios Paparizos[7], Dimitrios Chatzidimitriou[8], Dimitra Paraskeva[9], Pagona Lagiou[1], Angelos Hatzakis[1], Gkikas Magiorkinis[1], Lemonia Skoura[8], Dimitrios Paraskevis[1]

*[1]University of Athens, Athens, Greece, [2]Korgialeneio-Benakeio Red Cross General Hospital, Athens, Greece, [3]G. Gennimatas General Hospital, Athens, Greece, [4]Evaggelismos General Hospital, Athens, Greece, [5]Attikon General Hospital, University of Athens, Athens, Greece, [6]AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece, [7]A. Syngros Hospital of Dermatology and Venereology, Athens, Greece, [8]Aristotle University of Thessaloniki, Thessaloniki, Greece, [9]Tzaneio General Hospital of Piraeus, Piraeus, Greece*

**Background:** Our aim was to trace the geographic origin of HIV-1 subtype C and CRF02_AG infections, the most prevalent non-A1 and non-B clades in Greece, using molecular epidemiology methods.

**Methods:** Our study sample consisted of 146 HIV-1 subtype C and 139 CRF02_AG pol gene sequences of people living with HIV diagnosed between 1999 and 2015 in Greece. We analyzed phylogenetically the subtype C (N=78) and CRF02_AG (N=61) sequences from migrants along with all the available subtype C and CRF02_AG sequences from non-migrants. We also included a random set of globally sampled sequences (subtype C: 972; CRF02_AG: 858), and the most closely related sequences identified using the BLAST tool (subtype C: 50; CRF02_AG: 33), as references. Molecular transmission clusters (MTCs) were phylogenetic clusters including sequences from Greece at proportions >70%, receiving bootstrap value >75% and SH-support >0.9. Phylogenetic trees were estimated by the maximum likelihood method. The origin of HIV-transmissions was traced by phylogeographic analysis. Statistical analysis was based on multivariable logistic regression models for the investigation of parameters associated with clustering (STATA 13).

**Results:** Phylogenetic analysis revealed that 27 (34.6%) and 21 (34.4%) sequences from subtype C and CRF02_AG infected migrants clustered within MTCs. The size of MTCs ranged between 2 and 12 sequences for subtype C (21 MTCs in total) and 2 and 49 sequences for CRF02_AG (16 MTCs in total). Multivariable logistic regression analysis showed that parameters associated with clustering were the year of sampling for subtype C (OR: 1.25, 95% CI: 1.13-1.38) and Greek origin for subtype C (non-migrants vs migrants OR: 3.95, 95% CI: 1.65-9.48) and CRF02_AG (non-migrants vs migrants OR: 38.11, 95% CI: 8.09-79.44). Phylogeographic analysis showed that 23.3% of subtype C and 23.8% of CRF02_AG HIV-transmissions within migrants occurred in Greece.

**Conclusion:** We found that only 35% of subtype C and 34% of CRF02_AG infections within migrants were found in local networks in Greece and moreover that for both clades Greek origin was associated with infections within MTCs. In addition, we found that only a small proportion of subtype C (23%) and CRF02_AG (24%) HIV-transmissions within migrants originated in Greece. Our findings provide evidence that HIV-1 infections among migrants were not associated with onward transmission, thus suggesting that migrants did not impact the HIV epidemic in Greece.

## 784 DEEP LEARNING APPROACHES TO INFORM NETWORK-BASED HIV INTERVENTIONS AMONG PWID

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

*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]YR Gaitonde Center for AIDS Research and Education, Chennai, India*

**Background:** Globally, people who inject drugs (PWID) continue to experience some of the most explosive HIV epidemics. Network-based approaches are a powerful tool to understand transmission and implement interventions efficiently; however, detailed social network studies are limited and the non-Euclidian nature of networks poses analytical challenges. Advances in neural architectures in deep learning, namely graph neural networks (GNNs), offer new analytical tools to better elucidate network patterns to identify optimal intervention strategies.

**Methods:** We recruited a cohort of 2,512 PWID in New Delhi, India using a name generator network recruitment method that captured social (injection partners) and spatial (injection venues) network information. Biometric data was used to establish cross-network linkages. Longitudinal HIV incidence from November 2017 – March 2020 was 21.3 per 100 person-years (p-y). The Louvain algorithm was used to identify communities in the network i.e., groups of PWID and places they inject that are more connected to each other than other groups in the network. Neural Overlapping Community Detection (NOCD) using GNNs was used to determine community overlap.

**Results:** PWID reported injecting in 181 different injection venues across a diameter of over 20 km in New Delhi and formed one large network when accounting for social and spatial ties. Injection networks were highly dynamic (75% gained/lost a partner over a median 12 months of follow-up), but greater stability was observed in spatial networks (48% reported changing venues). Injecting at the highest risk venue (#40 in Fig) was the strongest predictor of incidence (adjusted incidence rate ratio [AIRR]= 3.11) and also exhibited the highest network stability (9% of those who injected at the venue switched venues). Seven distinct communities of PWID were identified. HIV incidence ranged from 0 – 40.9 per 100 p-y across these communities, with the highest incidence observed in community 3 (Fig). NOCD revealed that while only 2 of 2,512 person nodes overlapped >2 communities, 8 of 181 spatial nodes overlapped 6 of the 7 communities, suggesting that these 6 communities could be reached by rapidly scaling-up services in just one of these 8 venues.

**Conclusion: In** this setting with explosive HIV incidence, deep learning methods suggest network-based interventions that target spaces, which may represent unmeasured network connections, could be the optimal strategy to interrupt transmission among PWID while conserving resources.

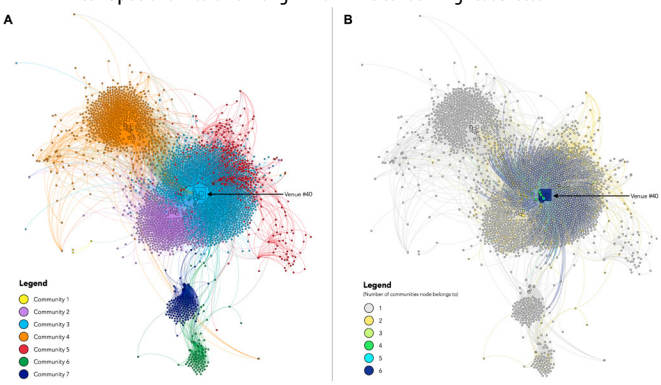



**Figure.** (A) Communities detected by modularity analysis of a sociospatial network of 2,512 people who inject drugs and 181 injection venues in New Delhi, India, and (B) the number of communities a node belongs to as identified by Neural Overlapping Community Detection. Circular nodes represent persons and square nodes represent venues. Nodes are sized by degree.

## 785 HIGH HIV INCIDENCE AMONG PWID ON THE US/MEXICO BORDER DURING THE COVID-19 PANDEMIC

**Britt Skaathun[1],** Cho-Hee Shrader[2], Annick Borquez[1], Antoine Chaillon[1], Tetyana Vasylyeva[1], Irina Artamanova[1], Alicia Harvey-Vera[1], Gudelia Rangel[1], Steffanie Strathdee[1]

*[1]University of California San Diego, La Jolla, CA, USA, [2]Columbia University, New York, NY, USA*

**Background:** In the U.S/Mexico border region, drug tourism (DT) has been linked to increased HIV risk among people who inject drugs (sharing injection equipment) and paying for sex. Sex and DT from the U.S. to Mexico drive bidirectional cross-border mobility, and have consequently played an important role in HIV spread in the border region, but prior to the COVID19 pandemic, HIV incidence remained <2 per 100 person years (PY). We assessed HIV incidence and associated risk factors among PWID during the COVID-19 pandemic.

**Methods:** Participants are from La Frontera, a longitudinal study of PWID aged ≥18 from 3 groups: PWID who injected drugs in Tijuana ≤24 months ago but live in San Diego (SD DTs), and non-drug tourist (NDT) PWID, who live in SD county or Tijuana (TJ) but have never used illicit drugs across the border. Beginning in Oct/2020, participants underwent surveys and provided samples for HIV and SARS-CoV-2 serology every 6 months, and an egocentric social network (SN) survey. HIV prevalence, bivariate incidence-density rates, incident rate-ratios (IRR), and exact 95% confidence intervals (CI) were calculated for independent variables between baseline and follow-up.

**Results:** To date, among 611 participants at baseline, HIV prevalence was 7.6% (SD DT: 3.8%, SD NDT: 3.5%, TJ NDT: 15.8%). Of the HIV- PWID returning for their

6 months visit thus far (n=286; 93% follow-up), eight HIV seroconversions occurred during 118 PY of follow-up (Incidence: 13.53/100PY; 95% CI: 5.84-26.66). Although not significant, incidence was notably higher among TJ NDT (19.9/100PY vs 1.82/100 PY SD DT vs 0 SD NDT; IRR 10.94, 95% CI 0.35, 22.59 TJ NDT vs SD DT), those who shared syringes/works with a network member (30.34/100PY vs. 7.31/100PY; IRR 4.15, 95% CI 0.37,9.19) and non-heterosexual participants (29.31/100PY vs 5.38/100PY; IRR 4.67, 95% CI 0.39, 9.67).

**Conclusion:** Preliminary HIV incidence rates among PWID in the U.S./Mexico border region during the pandemic are high, and suggest a new HIV outbreak among PWID residing in TJ. Mobile harm reduction services providing syringes and HIV testing, as well as coordination with the municipal HIV program to allow for ART initiation and PrEP are urgently needed to prevent a continuing outbreak.

**Predictors of incident HIV infection in 286 PWID over 6 months; La Frontera cohort, San Diego, US & Tijuana, MX, 2020–2021**

| | | HIV seroconversions | Person-years (PY) | Incidence Rate (95% CI) | Incidence Rate Ratio (95% CI) |
|---|---|---|---|---|---|
| **Overall** | Overall | 8 | 118.27 | 13.53 (5.84, 26.66) | -- |
| **Sample** | San Diego, Drug Tourist | 1 | 55.05 | 1.82 (0.05, 10.12) | ref |
| | San Diego, Not Drug Tourist | 0 | 22.83 | 0 (0, 16.16) | 0 |
| | Tijuana, Not Drug Tourist | 7 | 40.39 | 17.33 (6.97, 35.7) | 10.93 (0.35, 22.97) |
| **Race** | White | 1 | 40.84 | 2.45 (0.06, 13.64) | *ref* |
| | Black | 0 | 3.73 | 0 (0, 98.86) | 0 |
| | Hispanic | 3 | 52.7 | 5.69 (1.17, 16.63) | 3.11 (0.17, 15.74) |
| | Multi-Racial | 4 | 14.83 | 7.59 (2.07, 19.43) | 11.01 (0.32, 25.36) |
| | Other Race | 0 | 2.79 | 0 (0, 132.39) | 0 |
| **Age** | Age under 40 | 3 | 46.79 | 6.41 (1.32, 18.74) | *ref* |
| | Age over 40 | 5 | 71.48 | 7 (2.27, 16.32) | 1.31 (0.27, 4.71) |
| **Sexual Identity** | Heterosexual | 6 | 111.45 | 5.38 (1.98, 11.72) | *ref* |
| | Lesbian, Gay, or Bisexual | 2 | 6.82 | 29.31 (3.55, 105.88) | 4.67 (0.39, 9.67) |
| **Avoided prevention services in past 6 mo due to COVID** | Avoided prevention services | 1 | 18.35 | 5.45 (0.14, 30.37) | 1.83 (0.16, 10.79) |
| | Did not avoid prevention services | 6 | 99.33 | 6.04 (2.22, 13.15) | *ref* |
| **Frequency of injecting alone in past 6 mo compared to before COVID** | Inject alone more | 0 | 15.17 | 0 (0, 24.32) | 0 |
| | Inject alone less | 1 | 38.58 | 2.59 (0.07, 14.44) | 1.83 (0.16, 10.79) |
| | Inject alone the same | 6 | 62.89 | 9.54 (3.5, 20.76) | *ref* |
| **Network member is a drug tourist** | Has Drug Tourist in Network | 0 | 14.19 | 0 (0, 25.99) | 0 |
| | No Drug Tourist in Network | 8 | 104.08 | 7.69 (3.32, 15.15) | *ref* |
| **Ever shared syringe/works with network member** | Shared | 2 | 36.2 | 30.34 (0.77, 169.05) | 4.15 (0.37, 9.19) |
| | Did not Share | 6 | 82.07 | 7.31 (2.68, 15.91) | *ref* |
| **SARS-Cov-2 Genalyte Blood Test Result** | Negative | 3 | 69.42 | 4.32 (0.89, 12.63) | *ref* |
| | Positive | 2 | 25.24 | 7.92 (0.96, 28.63) | 1.83 (0.22, 7.79) |

## 786 MISSED OPPORTUNITIES: PREVENTION & CARE FOR PWID IN A WEST VIRGINIA HIV OUTBREAK

**Robert A. Bonacci**[1], Anne C. Moorman[1], Danae Bixler[1], McKenna Penley[1], Suzanne Wilson[2], Alana G. Hudson[2], Stephen Perez[1], Phillip P. Salvatore[1], Kathryn Curran[1], Rebecca Hershow[1], Alexandra M. Oster[1], Robert P. McClung[1]

*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]West Virginia Department of Health and Human Resources, Charleston, WV, USA*

**Background:** In 2019, the West Virginia (WV) Bureau for Public Health detected an increase in HIV diagnoses among people who inject drugs (PWID) in Kanawha County, an area disproportionately affected by the opioid crisis. Most HIV diagnoses occurred in healthcare settings among PWID aged 20–39 years who were experiencing homelessness. Our objective was to understand healthcare utilization and service delivery before and after HIV diagnosis among PWID in this outbreak.

**Methods:** For PWID residing in Kanawha County, WV with HIV diagnosed in the outbreak during 1/1/2019–6/18/2021, we searched inpatient and outpatient medical records from a large integrated medical system (including a Ryan White Part C Program) and a community clinic serving PWID. We abstracted and described data about diagnoses, substance use, medications, laboratory tests, and care setting during a review period from 1 year before HIV diagnosis through 6/18/2021; we determined HIV diagnosis and disease status from WV HIV surveillance data.

**Results:** We identified 496 encounters among 65 PWID during 127 person-years of follow-up (Table), including 17 (3%) encounters for overdose and 181 (36%) for injection drug use-associated bacterial infections. For 80 (26%) encounters, the patient left care against medical advice. Sixty-two HIV screening tests were performed during the review period. Twenty people (31%) were prescribed naloxone, 29 (45%) were prescribed medication for opioid use disorder (MOUD), 4 (6%) received syringe services, and 0 were prescribed HIV pre-exposure prophylaxis (PrEP). Emergency department (ED) and inpatient encounters declined following HIV diagnosis, whereas outpatient encounters increased (Table). Twelve PWID (18%) were ever diagnosed with AIDS, and 22 (34%) were ever virally suppressed.

**Conclusion:** Despite high healthcare utilization among PWID in this outbreak, we identified missed opportunities for the provision of HIV testing, PrEP, syringe services, MOUD, and naloxone. High utilization of ED and inpatient services indicates that acute care settings provide opportunities to engage PWID in essential prevention services. The high frequency of PWID leaving care against medical advice demonstrates a need to improve acute care service delivery for PWID. Enhanced integration of syringe services and MOUD in outpatient care, including HIV care, may improve engagement with routine preventive care, reduce burden on acute care facilities, and facilitate earlier HIV diagnosis and improved viral suppression.

Table. Characteristics of healthcare encounters among PWID in an HIV outbreak, by healthcare setting — Kanawha County, WV, 2019–2021[1]

| | Overall | Emergency Department | Inpatient | Outpatient |
|---|---|---|---|---|
| Healthcare encounters during review period (N, row %) | 496 (100%) | 207 (42%) | 100 (20%) | 189 (38%) |
| Healthcare encounters per patient (median, range) | 5 (1–33) | | | |
| Healthcare encounters per person-year before HIV diagnosis | 3.2 | 1.9 | 0.9 | 0.4 |
| Healthcare encounters per person-year after HIV diagnosis | 4.6 | 1.3 | 0.7 | 2.6 |
| Encounters with an IDU-associated bacterial infection (n, col %) | 181 (36%) | 75 (36%) | 77 (77%) | 29 (15%) |
| Encounters with a drug overdose diagnosis (n, col %) | 17 (3%) | 11 (5%) | 6 (6%) | 0 (0%) |
| Encounters in which syringe services provided (n, col %) | 4 (1%) | 0 (0%) | 0 (0%) | 4 (2%) |
| Opioid-related encounters[2] (n, col %) | 291 (59%) | 129 (62%) | 82 (82%) | 80 (42%) |
| Among opioid-related encounters[2], encounters with naloxone prescription documented (n, col %) | 28 (10%) | 4 (3%) | 12 (15%) | 12 (15%) |
| Among opioid-related encounters[2], encounters with MOUD prescription documented (n, col %) | 58 (20%) | 12 (9%) | 26 (32%) | 20 (25%) |

Abbreviations: col, column; IDU, injection drug use; MOUD, medication for opioid use disorder; n, number

[1]The outbreak investigation review period was 1/1/2019–6/18/2021

[2]Opioid-related encounters include all encounters in which a clinician documented illicit opioid use or prescription opioid misuse, a toxicology screen was positive for opioids, or syringe services were provided

## 787 EMPIRICAL ESTIMATES OF ADULT HIV INCIDENCE ACROSS 12 COUNTRIES IN SUB-SAHARAN AFRICA

**Nora E. Rosenberg**[1], Bonnie Shook-Sa[1], Mincen Liu[1], Lynda Stranix-Chibanda[2], Marcel Yotebieng[3], Nadia Sam-Agudu[4], Sam J. Phiri[5], Wilbroad Mutale[6], Linda-Gail Bekker[7], Manhattan E. Charurat[4], Jessica E. Justman[8], Benjamin Chi[1]

*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]University of Zimbabwe, Harare, Zimbabwe, [3]Albert Einstein College of Medicine, Bronx, NY, USA, [4]University of Maryland, Baltimore, MD, USA, [5]Partners in Hope, Lilongwe, Malawi, [6]University of Zambia, Lusaka, Zambia, [7]University of Cape Town, Cape Town, South Africa, [8]Columbia University, New York, NY, USA*

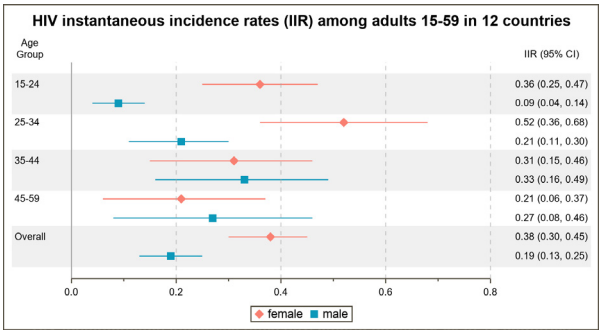
**Background:** Past estimates of HIV incidence in sub-Saharan Africa (SSA) have relied heavily on mathematical models and suggest important differences by age and sex. Population-based HIV Impact Assessment (PHIA) household surveys are now available to estimate HIV incidence empirically.

**Methods:** We analyzed publicly available data from PHIA surveys in 12 countries (Cameroon, Côte d'Ivoire, Eswatini, Ethiopia [urban regions], Namibia, Lesotho, Malawi, Rwanda, Tanzania, Uganda, Zambia, and Zimbabwe) to estimate incidence rates and number of new annual infections. Data were collected from surveys conducted from 2015-2019. Analysis was restricted to adults aged 15-59 years and disaggregated by age and sex. Recent infection was classified using a cross sectional algorithm consisting of HIV-1 Limited Antigen Avidity enzyme immunoassay, HIV-1 viral load, and antiretroviral detection. Data were pooled across countries and sampling weights were incorporated to represent adults in the full target population. All analyses accounted for the complex sample designs of the PHIA surveys. HIV instantaneous incidence rates (IIRs), IIR differences, 95% confidence intervals (CIs), and total number of new annual infections were estimated.

**Results:** Among 239,678 adults, 22,449 were HIV-1 seropositive and of these 290 had recent HIV infection. Overall HIV incidence was 0.38/100PYs (95% CI: 0.30, 0.45) among women and 0.19/100PYs (95% CI: 0.13, 0.25) among men (Figure 1). Among 15-24 year-old adolescents and young adults, IIRs were higher among women than men (0.36 vs. 0.09/100PYs; IIR difference: 0.27, 95% CI: 0.15, 0.39). Among 25-34 year-old adults, IIRs were also higher among women than men (0.52 versus 0.21/100PYs; IIR difference 0.31, 95% CI: 0.13, 0.49). IIRs were comparable between women and men 35-44 and 45-59 years old. Overall,

316,270 new annual HIV infections were estimated among adults aged 15-59 out of a target population of 121 million people in the 12 countries. Women in the two younger age groups (15-34 years) accounted for 52.5% of these new infections.

**Conclusion:** These analyses provide empiric estimates of the substantial burden of HIV in SSA and reinforce the differences by age and sex. Women aged 15-34 account for more than half of the new HIV infections in these 12 countries. Approaches for risk stratification by age, sex, and other factors can guide comprehensive HIV prevention services.




## 788 EDUCATION AND HIV RISK. EVIDENCE FROM 12 SUB-SAHARAN AFRICAN COUNTRIES. (2015–2018)

**Elizabeth Gummerson**[1], Daniela Quigee[2], Delivette Castor[3], Andrea Low[3]
*[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]Columbia University Medical Center, New York, NY, USA, [3]Columbia University, New York, NY, USA*

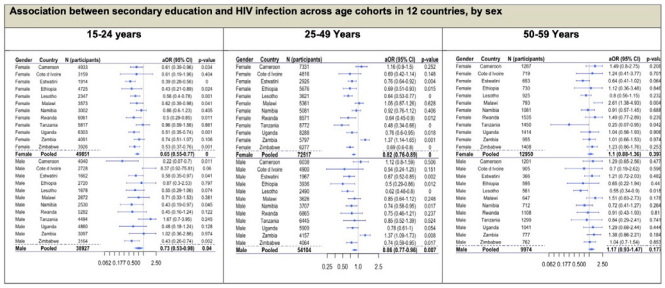
**Background:** Whether educational attainment is protective or a risk factor for HIV remains a subject of debate in the scientific literature. Early research showed a positive association between education and HIV. Some scholars predicted the education gradient would reverse over time, making education protective. We assessed associations between education and HIV prevalence and incidence using data from nationally representative population-based HIV impact assessment (PHIA) surveys in Zambia, Eswatini, Lesotho, Uganda, Tanzania, Malawi, Rwanda, Cote d'Ivoire, Cameroon, Zimbabwe, Ethiopia and Namibia

**Methods:** We used data on educational attainment from 134,116 women and 101,930 men 15 and older and paired it with respondents' HIV test results. Recent infection (<130 days) was measured using the HIV-1 Limiting Antigen (LAg) Avidity assay combined with viral load suppression (VLS, <1000 copies/mL) and antiretroviral (ARV) testing data. Recent infections were those with LAg<1.5 normalized Optical Density, VL>1000 copies/mL, and no detectable ARVs. We performed pooled analyses of the association between education and HIV prevalence and incidence on weighted data on adults aged 15–59 years, stratified by sex and age cohort, using logistic and poisson regression adjusted for age, urban residence, wealth quintile, country, employment status, marital status, household head gender.

**Results:** For women 15-24, secondary education was associated with lower odds of HIV infection in the pooled sample (adjusted odds ratio [aOR]: 0.65; 95% confidence interval [CI]: 0.55-0.75), with lower odds of HIV in all countries. For men 15-24, the association was also negative in the pooled sample (aOR: 0.73; CI: 0.53-0.98) but more variable by country. Among adults 25-49, the association was similarly negative for women (aOR: 0.82; CI: 0.76-0.89) and men (aOR: 0.86; CI: 0.77-0.96). The association reversed in the oldest cohort (50-59 years), with education positively but not significantly associated with HIV infection. There was no association between recent infection and education for men, but for women, having a secondary education was associated with about ¼ the risk of having recently been infected with HIV(aRR: 0.23; CI: 0.06-0.84)

**Conclusion:** Even when household wealth is accounted for, education is associated with lower risk of HIV in younger cohorts. The robustness of the association when other socioeconomic factors are accounted for suggests that the effect is independent of overall economic status.

**Figure. Secondary education and its association with HIV prevalence in sub-Saharan Africa (2015–2018).** Secondary education was defined as having attended at least secondary school, compared to only attending primary school or no formal education. Coefficients and confidence intervals based on weighted logistic regression including controls for marital status, wealth quintile, urban residence and age.




## 789 HEAVY RAINFALL IS ASSOCIATED WITH HIGHER HIV PREVALENCE ACROSS SUB-SAHARAN AFRICA

New Investigator Scholar

**Karly Hampshire**[1], Jason Nagata[1], Adrienne Epstein[1], Edwin D. Charlebois[1], Alexander C. Tsai[2], Denis Nash[3], Sheri D. Weiser[1]
*[1]University of California San Francisco, San Francisco, CA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]City University of New York, New York, NY, USA*

**Background:** Extreme precipitation, including heavy rains and flooding, is associated with poor health outcomes mediated by shocks to income and food production. No previous studies have examined associations between extreme precipitation and HIV prevalence. We evaluated the association between heavy rainfall and HIV prevalence, as well as HIV risk behaviors, over a 21 year span in sub-Saharan Africa, a region disproportionately impacted by both climate change and HIV.

**Methods:** We used data from Demographic and Health Surveys (DHS) in 21 countries in sub-Saharan Africa spanning 1997-2017 (288,333 respondents aged 15-59). Heavy rainfall was categorized as an annual standardized precipitation index of ≥1.5. We summed the number of heavy rainfall years a participant was exposed to at the enumeration area level in the 10 years prior to the survey. We estimated the association between years of heavy rains and HIV prevalence, self-reported sexually transmitted infections (STIs) and multiple sexual partnerships using multivariable regression models with survey fixed effects and robust standard errors, adjusting for sex, marital status, age, education, wealth index, urban/rural residence, and month. We also assessed effect modification by sex, urban/rural location, and age.

**Results:** Each year of heavy rain was associated with 1.14 (95% CI 1.11, 1.18) times the odds of HIV infection and 1.11 (95% CI 1.07, 1.15) times the odds of an STI in the past 12 months. There was also a positive association between heavy rain and reported number of sexual partners (incident rate ratio = 1.12, 95% CI 1.06-1.17). Associations were observed in both males and females, in rural and urban settings, and among adolescents and adults, though there were differences in specific associations by subgroup (see Table 1).

**Conclusion:** Heavy rainfall was associated with higher HIV burden in sub-Saharan Africa. The association between heavy rainfall and STIs and number of sexual partners suggests that increased sexual risk taking is a plausible mechanism for the observed findings. Other possible explanatory pathways include heavy precipitation causing food insecurity leading to transactional sex, or health infrastructure damages reducing access to STI education. This work adds to a growing body of evidence on the deleterious health impacts of extreme weather events.

**Table 1. Adjusted odds ratios for the associations between heavy rainfall and HIV/sexual risk-taking outcomes, stratified by sex, rural/urban, and age category.**

| Outcome | | HIV Prevalence | STI in the past 12 months | Number of sexual partners in the past 12 months |
|---|---|---|---|---|
| Stratified by sex | Male | 1.13 (1.08-1.18)*** | 1.03 (0.98-1.09) | 1.14 (1.09-1.19)*** |
| | Female | 1.15 (1.11-1.19)*** | 1.15 (1.10-1.20)*** | 1.10 (1.01 - 1.19)* |
| | Interaction P | 0.01 | 0.48 | 0.36 |
| Stratified by rural/urban | Rural | 1.21 (1.16-1.27)*** | 1.19 (1.13-1.25)*** | 1.09 (1.01 - 1.17)* |
| | Urban | 1.10 (1.05-1.16)*** | 1.02 (0.97-1.07) | 1.14 (1.07 - 1.22)*** |
| | Interaction P | <0.001 | 0.01 | 0.02 |
| Stratified by age category | Adolescent | 1.14 (1.04-1.25)*** | 0.99 (0.89-1.10) | 1.11 (1.03 - 1.19)** |
| | Adult | 1.14 (1.11-1.18)*** | 1.12 (1.08-1.16)*** | 1.12 (1.06 - 1.19)*** |
| | Interaction P | <0.001 | <0.001 | 0.02 |

All models control for sex, marital status, age, education (none, primary, secondary, and higher), wealth index, urban residence, and survey month. Standard errors are clustered at the EA level. Asterisks denote level of significance ***p<0.001 **p<0.01 *p<0.05.

## 790 HIV RISK BEHAVIORS AMONG BLACK AND HISPANIC TRANSGENDER WOMEN IN THE UNITED STATES

New Investigator Scholar

**Xinyi Li**[1], Evelyn J. Olansky[2], Kathryn Lee[3], Janet Burnett[3]
*[1]Oak Ridge Institute for Science and Education, Atlanta, GA, USA, [2]ICF International, Atlanta, GA, USA, [3]Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** HIV prevalence is high among transgender women in the United States. Within National HIV Behavioral Surveillance among Transgender Women (NHBS-Trans), 62% of Black and 35% of Hispanic transgender women tested positive for HIV. Risks associated with HIV by race/ethnicity are understudied, especially sexual behavior risks. We investigated HIV testing and pre-exposure prophylaxis (PrEP) uptake in the last 12 months and sexual behaviors with last sex partner among Black and Hispanic transgender women in NHBS-Trans.
**Methods:** Transgender women from 7 U.S. cities were recruited using respondent-driven sampling (RDS), interviewed, and offered HIV testing. Participants aged 18 years or older, who resided in a participating city, did not previously participate in the survey, spoke English or Spanish, provided informed consent, self-identified as women or transgender women, were assigned male or intersex at birth, and tested negative for HIV were included. We used log-linked Poisson regression models, adjusted for RDS design, age, education, and 2019 poverty level, to calculate adjusted prevalence ratios (aPR) and 95% confidence intervals (CI).
**Results:** Among transgender women who tested negative for HIV (n=901), Black and Hispanic transgender women were more likely than white/other race transgender women to report a cisgender man as their last sex partner (aPR: 1.31, 95%CI: 1.16-1.47; aPR: 1.22, 95%CI: 1.10-1.34), concurrent partners (aPR: 1.35, 95%CI: 1.05-1.74; aPR: 1.29, 95%CI: 1.10-1.52), and condomless sex at last sex (aPR: 1.40, 95%CI: 1.03-1.91; aPR: 1.49, 95%CI: 1.15-1.92). Hispanic transgender women were more likely to report condomless sex at last sex with a partner that had a positive or unknown HIV status (aPR: 1.83, 95%CI: 1.26-2.68), HIV testing (aPR: 1.10, 95%CI: 1.03-1.19) and PrEP use (aPR: 1.50, 95%CI: 1.14-1.96) in the last 12 months compared to their white/other race counterparts. No difference was found in HIV testing and PrEP between Black and white/other transgender women.
**Conclusion:** Despite equivalent or greater utilization of HIV testing and PrEP, Black and Hispanic transgender women may face higher HIV risks through sexual behaviors than white/other race transgender women. Further investigation of contributing factors is needed, including structural factors that may influence behaviors. HIV prevention programs should take behaviors into account when tailoring programs to reduce HIV risks among Black and Hispanic transgender women.

## 791 GENDER IDENTITY, STIGMA, AND SEXUALLY TRANSMITTED INFECTIONS IN NIGERIA

**Elyse LeeVan**[1], Fengming Hu[1], Andrew Mitchell[2], Afoke Kokogho[3], Sylvia Adebajo[4], Haoyu Qian[1], Julie Ake[1], Merlin Robb[5], Manhattan E. Charurat[2], Stefan Baral[6], Rebecca G. Nowak[2], Trevor A. Crowell[1]
*[1]US Military HIV Research Program, Silver Spring, MD, USA, [2]Institute of Human Virology, University of Maryland, Baltimore, MD, USA, [3]HJF Medical Research International, Abuja, Nigeria, [4]Center for International Health and Biosecurity (Ciheb), Abuja, Nigeria, [5]Henry M Jackson Foundation, Bethesda, MD, USA, [6]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*

**Background:** Sexual and gender minority populations are disproportionately affected by the global syndemic of HIV and other sexually transmitted infections (STIs). We evaluated associations between gender identity and STIs, sexual behaviors, and stigma among people vulnerable to STIs in Nigeria. We hypothesized that transgender women (TGW) are more vulnerable to stigma and STIs than cis-gender men who have sex with men (cis-MSM).
**Methods:** From 2013-2020 the TRUST/RV368 cohort enrolled adults assigned the male sex at birth who reported anal sex with men in Abuja and Lagos, Nigeria. At three-monthly visits, participants were tested for STIs and completed questionnaires to assess sexual behaviors and social stigma. Participants were categorized as cis-MSM, TGW, or non-binary/other based on self-reported gender identity. Gender group comparisons were made of HIV, gonorrhea, and chlamydia prevalence and incidence; stigma indicators; and condom use during anal sex.
**Results:** Among 2795 participants, there were 2260 (80.8%) cis-MSM, 284 (10.2%) TGW, and 251 (9.0%) non-binary/other individuals with median age of 23 years (interquartile range 20-27). HIV prevalence among cis-MSM, TGW, and non-binary/other participants was 40.8%, 51.5%, and 47.6%, respectively (p=0.001). As compared to cis-MSM, TGW had a higher incidence of HIV and lower incidence of anorectal gonorrhea; HIV incidence was highest among non-binary/other participants (Figure). TGW were more likely than cis-MSM to report being affected by stigma, including healthcare avoidance (25.0% vs. 19.1%), fear of walking around (32.4% vs. 19.2%), and assault (47.2% vs. 32.3%; all p<0.05). Always using condoms during insertive anal sex was reported by 33.4% of cis-MSM, 19.5% of TGW, and 28.7% of non-binary/other participants (p<0.001), and during receptive anal sex by 22.6%, 32.9%, and 22.1% (p<0.001), respectively.
**Conclusion:** Sexual and gender minority populations in Nigeria have heterogenous sexual behaviors and experiences of social stigma that may influence vulnerability to HIV and other STIs. Particularly high HIV incidence, higher stigma, and differential condom use among TGW and non-binary/other participants suggests a need for targeted and gender-affirming prevention interventions. Collection of gender identity data in research is necessary to better understand disparities among sexual and gender minorities and and inform tailored interventions to improve outcomes among these communities in Nigeria.

**Figure: Trust study HIV/STI summary by Gender**

| | Cisgender men | | | Transgender women | | | Nonbinary/Other | | |
|---|---|---|---|---|---|---|---|---|---|
| | Prevalence | Incidence | | Prevalence | Incidence | | Prevalence | Incidence | |
| | % | Cases/100PY | 95% CI | % | Cases/100PY | 95% CI | % | Cases/100PY | 95% CI |
| HIV | 40.8 | 8.7 | 6.9 - 10.8 | 51.5 | 13.1 | 6.5 - 23.4 | 47.6 | 17.6 | 9.8 - 29.0 |
| Neisseria gonorrhoeae | | | | | | | | | |
| Anorectal | 17.2 | 22.2 | 19.6 - 25.0 | 29.1 | 35.9 | 27.3 - 46.3 | 22.2 | 20.4 | 13.5 - 29.7 |
| Urogenital | 3.6 | 4.3 | 3.3 - 5.5 | 2.3 | 2.6 | 1.0 - 5.7 | 3.1 | 3.5 | 1.3 - 7.5 |
| Oropharyngeal | 5.7 | 10.7 | 8.7 - 12.9 | 9.4 | 15.2 | 9.4 - 23.3 | 0.9 | 9.1 | 4.4 - 16.8 |
| Chlamydia trachomatis | | | | | | | | | |
| Anorectal | 12.5 | 19.7 | 17.3 - 22.2 | 13.1 | 26.3 | 19.4 - 34.9 | 17.3 | 22.4 | 15.3 - 31.6 |
| Urogenital | 5.0 | 7.9 | 6.5 - 9.4 | 7.5 | 7.3 | 4.2 - 11.8 | 2.5 | 3.8 | 1.5 - 7.8 |
| Oropharyngeal | 2.6 | 6.4 | 4.9 - 8.1 | 4.5 | 6.1 | 2.8 - 11.6 | 0.9 | 6.4 | 2.6 - 13.2 |

## 792 PREVALENCE OF UNTREATED HIV AND HIV INCIDENCE AMONG OCCUPATIONAL GROUPS IN UGANDA

**Victor O. Popoola**[1], Joseph Kagaayi[2], Joseph Ssekasanvu[1], Robert Ssekubugu[2], Anthony Ndyanabo[2], Fred Nalugoda[2], Larry W. Chang[1], Godfrey Kigozi[1], Justin Lessler[1], Maria Wawer[1], Donna Kabatesi[3], Lisa Mills[3], Steven J. Reynolds[4], David Serwadda[2], M. Kate Grabowski[1]
*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]Rakai Health Sciences Program, Kalisizo, Uganda, [3]Centers for Disease Control and Prevention, Kampala, Uganda, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** In sub-Saharan Africa, certain occupations have been associated with a heightened risk of HIV acquisition and spread, including bar/restaurant work and transportation (eg, trucking). However, data on changes in the prevalence of untreated HIV and HIV incidence within occupations during scale-up of combination HIV prevention and treatment (CHP), including antiretroviral therapy (ART) and voluntary medical male circumcision, are limited.
**Methods:** This study included 12 rounds of survey data collected during 1999-2016 from the Rakai Community Cohort Study, a population-based study of persons 15–49 years in Uganda, to assess changes in the prevalence of untreated HIV and HIV incidence by participants' self-reported primary occupation. Untreated HIV was defined using data on self-reported ART use and HIV seropositivity, and incidence from paired HIV serologies. Adjusted prevalence risk ratios (PRR) for untreated HIV and incidence rate ratios (IRR) for HIV infection with 95% confidence intervals (CIs) were estimated using Poisson regression with adjustment for age and marital status. Prevalence of occupations and untreated HIV were assessed at each visit and incidence over three time periods (pre CHP: 1999–2004; early CHP: 2005–2011; late CHP: 2011–2016).
**Results:** There were 33,866 individuals who participated, including 19,113 (56%) women. Of these, 8,308 men and 9,502 women were HIV-negative at study entry and contributed 8,421 and 10,771 person-years to the incidence cohort, respectively. Agriculture was the most commonly reported occupation irrespective of sex, but its prevalence declined from 61 to 40% among women and from 39 to 29% among men over the analysis period. Prevalence of untreated HIV declined in most occupations, including among men working in agriculture by 70% (12% to 4.2%; adjPRR=0.30 [95% CI 0.23-0.41]; p<0.001) and among women working in agriculture by 78% (15% to 4.0%; adjPRR=0.22 [95% CI 0.18-0.27]; p<0.001). There was evidence of HIV incidence declines in

most occupations (Table), but with exceptions, including among men working in transportation and women working in bars/restaurants.

**Conclusion:** While HIV burden has declined in most occupations, untreated prevalence and incidence remains relatively high and or unchanged in some occupations. Prevention and treatment programs tailored to meet the needs of persons working in higher risk occupations, such as transportation and bar/restaurant work, may improve HIV control.

**Table**. Incidence of HIV infection by occupational subgroup, sex, and CHP (combination HIV prevention) calendar period in the RCCS, 1999-2016.

| | Men (N=8,308) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Incidence rate per 100 py (n/py) | | | IRR (95% CI) | | adjIRR (95%CI) | |
| Occupation | Pre – CHP (1999-2004) | Early – CHP (2004-2011) | Late – CHP (2011-2016) | Early – CHP vs. Pre-CHP (ref) | Late – CHP vs Pre-CHP (ref) | Early – CHP vs. Pre-CHP (ref) | Late – CHP vs Pre-CHP (ref) |
| Agriculture | 1.2 (53/4401) | 0.7 (62/9161) | 0.4 (25/6745) | 0.56* (0.39 – 0.81) | 0.31* (0.19 – 0.50) | 0.58* (0.40 – 0.84) | 0.33* (0.21 – 0.54) |
| Construction | 1.4 (18/1261) | 1.1 (28/2612) | 0.5 (9/1054) | 0.75 (0.42 – 1.36) | 0.32* (0.15 – 0.72) | 0.79 (0.43 – 1.46) | 0.36* (0.15 – 0.83) |
| Trading/vending | 0.8 (13/1706) | 0.6 (26/4098) | 0.5 (15/3150) | 0.83 (0.43 – 1.62) | 0.63 (0.30 – 1.32) | 0.88 (0.46 – 1.70) | 0.69 (0.33 – 1.45) |
| Casual labor | 0.9 (3/310) | 1.3 (7/522) | 0.5 (2/428) | 1.43 (0.37 – 5.54) | 0.50 (0.08 – 3.00) | 1.66 (0.42 – 6.54) | 0.67 (0.11 – 4.21) |
| Government/Clerical/ Teaching | 0.7 (7/1066) | 0.5 (12/2306) | 0.3 (6/1798) | 0.79 (0.31 – 2.02) | 0.51 (0.17 – 1.51) | 0.78 (0.31 – 1.99) | 0.49 (0.16 – 1.51) |
| Student | 0.1 (1/955) | 0.05 (1/1910) | 0.1 (3/2863) | 0.50 (0.03 – 8.00) | 1.00 (0.10 – 9.63) | 0.51 (0.03 – 8.22) | 0.44 (0.04 – 4.86) |
| Mechanic | 0.0 (0/259) | 0.09 (8/8670) | 0.4 (4/949) | - | - | - | - |
| Transportation | 1.3 (4/306) | 1.6 (21/1346) | 1.0 (12/1171) | 1.19 (0.41 – 3.48) | 0.78 (0.25 – 2.43) | 1.32 (0.45 – 3.87) | 1.10 (0.35 – 3.45) |
| | Women (N=9,602) | | | | | | |
| | Incidence rate per 100 py (n/py) | | | IRR (95% CI) | | adjIRR (95%CI) | |
| | Pre – CHP (1999-2004) | Early – CHP (2004-2011) | Late – CHP (2011-2016) | Early – CHP vs. Pre-CHP (ref) | Late – CHP vs Pre-CHP (ref) | Early – CHP vs. Pre-CHP (ref) | Late – CHP vs Pre-CHP (ref) |
| Agriculture | 1.0 (97/9653) | 0.8 (120/16340) | 0.5 (62/11639) | 0.79 (0.60 – 1.02) | 0.53* (0.39 - 0.73) | 0.87 (0.67 – 1.13) | 0.62* (0.45 - 0.86) |
| Bar/Restaurant Owner/Worker | 0.0 (4/509) | 1.4 (17/1227) | 1.2 (12/1006) | 1.76 (0.59 – 5.24) | 1.52 (0.49 – 4.71) | 2.12 (0.72 – 6.23) | 2.74 (0.85 - 8.83) |
| Trading/Vending | 1.1 (17/1512) | 1.1 (49/4309) | 0.6 (23/3881) | 1.01 (0.50 - 1.76) | 0.53* (0.28 – 0.99) | 1.18 (0.69 – 2.04) | 0.72 (0.38 - 1.36) |
| Hair Dressing | 1.8 (3/166) | 1.3 (10/794) | 0.6 (6/932) | 0.70(0.19 – 2.55) | 0.36 (0.09 – 1.43) | 0.73 (0.20 - 2.64) | 0.36 (0.09 – 1.42) |
| Government/Clerical/ Teaching | 1.0 (9/922) | 0.5 (14/2712) | 0.2 (5/2148) | 0.53 (0.23 - 1.22) | 0.24* (0.08 – 0.71) | 0.76 (0.31 - 1.85) | 0.49 (0.13 - 1.77) |
| Student | 0.3 (2/636) | 0.4 (6/1441) | 0.7 (14/2153) | 1.32 (0.27 – 6.56) | 2.07 (0.47 - 9.10) | 1.23 (0.25 – 6.09) | 1.02 (0.44 – 8.32) |
| House Keeping | 1.0 (6/583) | 0.9 (15/1654) | 0.8 (12/1515) | 0.88 (0.34 2.28) | 0.77 (0.29 2.06) | 0.99 (0.37 2.65) | 0.89 (0.30 2.57) |
| Local Crafts | 1.1 (5/446) | 1.8 (12/654) | 1.3 (5/393) | 1.64 (0.58 – 4.66) | 1.14 (0.33 – 3.93) | 1.86 (0.65 – 5.33) | 1.34 (0.38 – 4.81) |
| Tailoring/Laundry | 1.5 (2/134) | 1.2 (5/406) | 0.9 (3/316) | 0.83 (0.16-4.28) | 0.64 (0.11-3.83) | 0.94 (0.17-5.02) | 0.85 (0.15-4.78) |

py=person years; IRR=incidence rate ratio; adjIRR=adjusted incidence rate ratio for age and marital status; CHP=combination HIV prevention
*p<0.05

## 793 MEDIATORS OF HIV/STI IN NON–US-BORN VS US-BORN HETEROSEXUAL ADULTS IN 22 US CITIES

**Laura Platt**[1], Fatma M. Shebl[2], Katherine K. Hsu[3], Kevin L. Ard[2], Catlainn Sionean[4], Johanna Chapin-Bardales[4], Bridget A. Bunda[5], Ingrid V. Bassett[2], Monina Klevens[3]

*[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Massachusetts Department of Public Health, Boston, MA, USA, [4]Centers for Disease Control and Prevention, Atlanta, GA, USA, [5]Tulane University, Metairie, LA, USA*

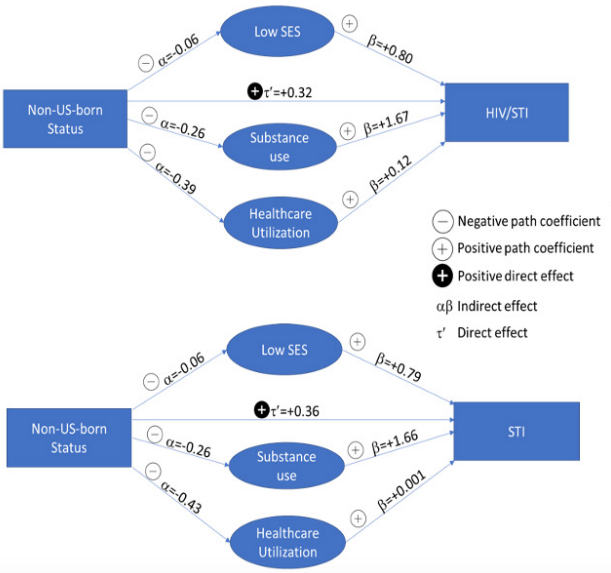
**Background:** Nearly a quarter of new HIV diagnoses in the United States are attributed to heterosexual transmission. Among heterosexually active people, non-US-born adults are diagnosed with HIV at higher rates than US-born. We analyzed data from the heterosexual cycle of National HIV Behavioral Surveillance (NHBS) (2013, 2016, 2019) to evaluate associations between place of birth and HIV/STI.

**Methods:** NHBS is a cross-sectional survey conducted in US cities with high HIV prevalence. Heterosexually active men and women of low income were recruited via respondent driven sampling and interviewed. We used structural equation modeling to test if socioeconomic status (SES), substance use, and healthcare utilization mediate the association between non-US-birth and self-reported HIV/STI (diagnosed with HIV [ever] or a bacterial STI [gonorrhea or syphilis, past year]). We deconstructed the relationship between non-US-birth and HIV/STI into: 1) the direct effect, the path from non-US-birth to HIV/STI and 2) the indirect (mediated) effect, the path from non-US-birth to HIV/STI through mediators.

**Results:** The sample included 32525 participants among whom 15818 (48.6%) were male, 1584 (4.9%) were non-US-born, 2287 (7.0%) had STI and 2993 (9.2%) had HIV/STI. HIV/STI was lower among non-US-born (6.4%) than US-born (9.4%). Non-US birth had a direct effect on HIV/STI ($\tau'$=0.32; p <.001) and substance use, low SES, and high health care utilization were associated with higher HIV/STI. However, non-US-born respondents had lower substance use ($\alpha$= -0.26; p <.001), higher SES ($\alpha$= 0.06; p <.001), and lower health care utilization ($\alpha$= -0.39; p <.001) than US-born. Substance use accounted for the highest percent of the mediated effect (48.6%). Restricting the outcome to STI alone did not change results (Figure 1).

**Conclusion:** Unexpectedly, non-US-born individuals reported lower HIV/STI. This was due to mediation, with non-US-born respondents having less substance use, higher SES, and lower health care utilization. Substance use accounted for the greatest discrepancy in HIV/STI between US-born and non-US-born respondents, such that higher substance use among US-born participants was associated with greater self-reported HIV/STI. Among low income heterosexually active adults living in high HIV-burden cities, non-US-birth is associated with protective factors for HIV/STI that warrant further study.

Figure 1: Models of the association between non-US-born status and HIV/STI (top) and STI alone (bottom)




## 794 SOURCES OF HIV TRANSMISSION IN THE ERA OF UNIVERSAL TEST AND TREAT: A MODELING STUDY

**Adam Akullian**[1], Joshua Herbeck[1], Anna Bershteyn[2]

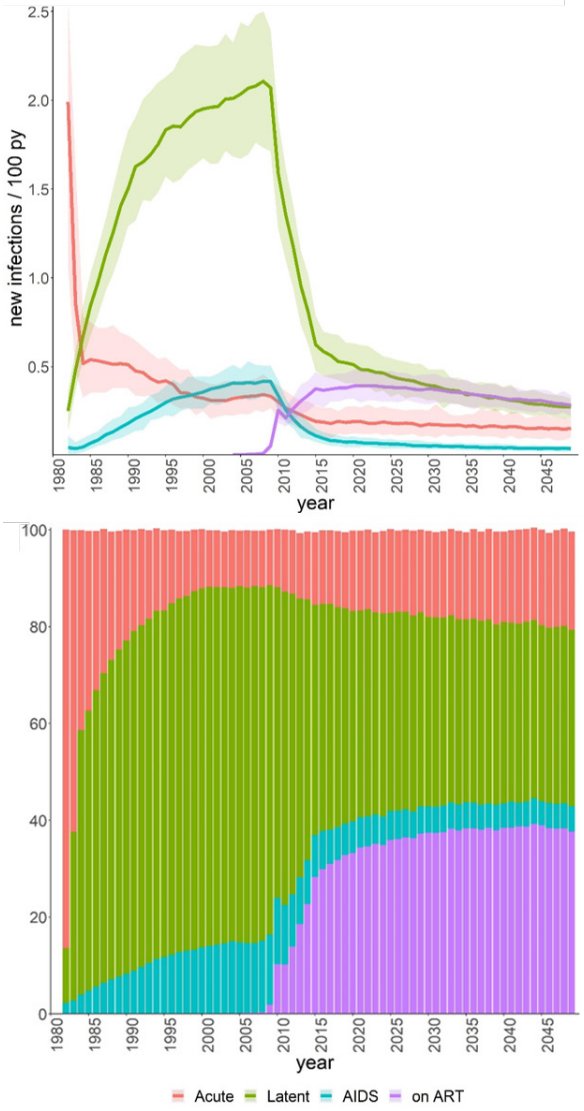
*[1]Bill and Melinda Gates Foundation, Seattle, WA, USA, [2]New York University, New York City, NY, USA*

**Background:** The scale-up of antiretroviral therapy (ART) in sub-Saharan Africa (SSA) over the last decade has contributed to substantial declines in HIV risk and mortality, yet incidence remains high (> 1%) across regions of eastern and southern Africa. Identifying the sources of persistent transmission in the era of universal test and treat (UTT) will be necessary to prioritize further interventions to drive incidence towards epidemic control.

**Methods:** We used a stochastic, agent-based epidemic model, calibrated to the HIV epidemic in the Kingdom of eSwatini (formerly Swaziland) to estimate the contribution to incidence (per 100 uninfected person-years and as a proportion of total incidence) by demographic group (age and sex), stage of infection (acute (<3 months from infection), early (<1 year from infection), latent (between 3 months from infection to AIDS stage), AIDS), and state in cascade of care (undiagnosed, diagnosed but never initiated on ART, on ART, disengaged from ART, and re-engaged on ART).

**Results:** Our model suggests that ART scale-up to date (2020) has had the largest effect on reducing transmissions from PLHIV in the latent stage through the direct suppression of viral load in those individuals. Prior to the large-scale expansion of ART (before 2010) transmissions from PLHIV in the latent (but ART naïve) stage accounted for 70% of adult HIV incidence (2 per 100 py). Following UTT scale-up the contribution from PLHIV in the latent stage declined to 0.5 per 100 py (<50% of overall incidence). Transmission from acutely infected PLHIV before ART scale-up accounted for 10% of total incidence (<0.5 infections per 100 py) and declined to 0.25 per 100 py after ART scale-up, though made up a growing fraction of all transmissions after 2010 (~20%). By 2030, our model projects that 50% of all HIV acquisitions in young men (<25) will come from women who had been infected for less than one year and 40% of all HIV acquisitions in young women (<25) will come from men who had been infected for less than one year. Transmissions from those on ART fraction will make up 40% of all transmissions in the UTT era and account for a majority of transmissions among men and women > age 25 years.

**Conclusion:** HIV transmissions from PLHIV currently on ART and from those in from PLHIV in the acute and early stages of infection contribute a growing fraction of transmissions as ART coverage reaches global targets. Targeted HIV prevention will be necessary to close the incidence gap in the UTT era.




## 795 HIV INCIDENCE AND IMPACT OF INTERVENTIONS IN FEMALE SEX WORKERS IN MENA

**Hiam Chemaitelly**[1], Houssein H. Ayoub[2], Ryosuke Omori[3], Shereen El Feki[4], Joumana G. Hermez[5], Helen A. Weiss[6], Laith J. Abu-Raddad[1]
*[1]Weill Cornell Medicine College in Qatar, Doha, Qatar, [2]Qatar University, Doha, Qatar, [3]Hokkaido University, Sapporo, Japan, [4]The Joint United Nations Programme on HIV/AIDS, Cairo, Egypt, [5]World Health Organization Regional Office for the Eastern Mediterranean, Cairo, Egypt, [6]London School of Hygiene & Tropical Medicine, London, UK*

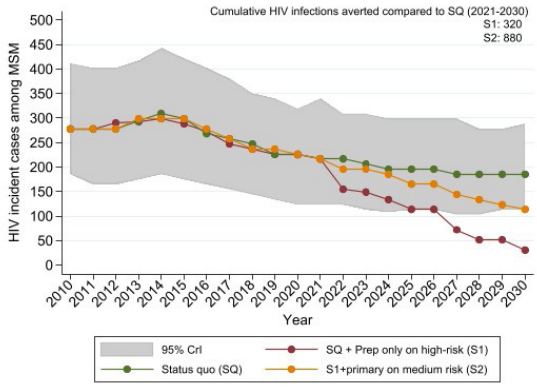
**Background:** HIV incidence among female sex workers (FSWs) and clients in the Middle East and North Africa (MENA) is unknown. Incidence, contribution of heterosexual sex work networks (HSWNs) to the epidemic, and impact of interventions were assessed in MENA countries using mathematical modeling.
**Methods:** A novel individual-based model to simulate HIV epidemic dynamics in HSWNs was developed and applied to 12 MENA countries with sufficient data. Model input parameters were provided through a systematic review of HIV prevalence, sexual and injecting behaviors, and risk group size estimates of FSWs and clients.
**Results:** The estimated number of new infections in 2020 in the 12 countries was 3,471 (range: 1,295-10,308) among FSWs, 6,416 (range: 3,144-14,223) among clients, and 4,717 (range: 3,490-7,288) among client spouses. These infections accounted for 25.1% of total HIV incidence in the MENA region. Contribution of incidence in HSWNs to total incidence ranged from 3.3% in Pakistan to 71.8% in South Sudan and 72.7% in Djibouti. Incidence in HSWNs was distributed equally among FSWs, clients, and client spouses. Estimated incidence rates among FSWs, per 1,000 person-years, ranged from 0.4 (95% CI: 0.0-7.1) in Yemen to 34.3 (95% CI: 17.2-59.6) in South Sudan. Among FSWs who inject drugs, estimated incidence rates, per 1,000 person-years, ranged from 5.1 (95% CI: 0.0-35.1) in Iran to 45.8 (95% CI: 0.0-428.6) in Pakistan. All interventions substantially reduced incidence among FSWs, clients, and client spouses. Even when a subpopulation did not benefit directly from an intervention, it still benefited indirectly through reduction in onward transmission. The indirect impact was often half as large as the direct impact.
**Conclusion:** Substantial HIV incidence occurs in HSWNs across MENA with client spouses being heavily affected, in addition to FSWs and clients. Rapidly scaling up comprehensive treatment and prevention services for FSWs can sizably reduce incidence arising in HSWNs.

## 796 ASSOCIATION THE HIV STATUS OF HOUSEHOLD HEAD AND THEIR YOUTHS IN 10 AFRICAN COUNTRIES

Late Breaking

**Matthew A. Weisberg**[1], Mansoor Farahani[2], Rachel Bray[2], Jessica E. Justman[2], Wafaa M. El-Sadr[2]
*[1]Columbia University, New York, NY, USA, [2]ICAP at Columbia University, New York, NY, USA*

**Background:** HIV prevalence remains high among youths (15-24 years old) in Sub-Saharan Africa; however, little is known regarding the association of parents and youth's HIV status, beyond the focus on mother-to-child transmission (MTCT). We examined the association between the HIV status of the household head (HH) and the youths in the household and their risky sexual behavior, using the Population-Based HIV Impact Assessment (PHIA) surveys conducted (2015-2019) by ministries of health in collaboration with ICAP at Columbia University and CDC.
**Methods:** Consenting adults from randomly selected households in 10 African countries provided demographic and behavioral information and blood samples for HIV testing. We applied multivariable Poisson regression using survey weights. Variances were estimated via Taylor series linearization.
**Results:** We examined data from 52,498 youths aged 15-24 and 34,051 HHs. Among HHs, 4,234 (12.4%) were HIV+ (7.3% female HHs, 5.1% male HHs). HIV prevalence among adolescents (15-19) and young adults (20-24) with an HIV+ HH was 4.7% and 13.0%, respectively. In contrast, HIV prevalence among those in the same age groups, but with the HIV- HH, was 0.9% and 2.0%, respectively. Controlling for other covariates, adolescents and young adults were more likely to be HIV+ if the HH was HIV+, with an adjusted prevalence ratio (aPR) of 3.4 (95% CI: 2.8-4.1) and 3.6 (95% CI 3.2-4.2), respectively. Moreover, females aged 15-24 had significantly higher aPR (3.6 [95% CI: 3.1-4.0]) than males (2.9 [95% CI 2.3-3.7]). Adolescents and young adults were more likely to have more than one sex partner in the 12 months before the survey if their HHwas HIV+, with aPR 1.1 (95% CI: 1.0-1.3) and 1.2 (95% CI: 1.1-1.3) respectively (Table).
**Conclusion:** The findings from 10 African countries indicate a strong association between the HIV status of the HH and the youths in the household and with more risky sexual behavior. The consistent pattern across these countries motivates focus on HIV prevention efforts for youths residing with HIV+ HHs. The difference in prevalence among youth by sex supports higher risk is due to sexual transmission rather than MTCT.




## 797 GREEK MSM: 95-95-95 TARGET IS NOT ENOUGH TO MEET THE HIV INCIDENCE REDUCTION GOAL

**Ilias Gountas[1],** Kyriakos Souliotis[1], Georgios Nikolopoulos[2], Giota Touloumi[3]
*[1]University of Peloponnese, Korinthos, Greece, [2]University of Cyprus, Nicosia, Cyprus, [3]National and Kapodistrian University of Athens, Athens, Greece*

**Background:** The 95-95-95 strategy aims to end the AIDS epidemic by 2030 by diagnosing 95% of all people living with HIV (PLHIV), by administering antiretroviral therapy (ART) to 95% of the diagnosed, and by achieving viral suppression (VS) on 95% of those on ART. UNAIDS modeling predictions suggest that those targets could reduce the HIV incidence worldwide by 90% in 2030 compared to 2010. However, several studies have underlined that in high-income countries, HIV cascade of care (CoC) targets may be insufficient to achieve the incidence goal and that additional interventions, like pre-exposure prophylaxis (PrEP), will be needed. In Greece, HIV infection is more prevalent among men who have sex with men (MSM), accounting for about half of all annual diagnoses. This study aims: a) to estimate the expected reduction in HIV incidence under the status quo scenario by 2030 and b) to highlight the required healthcare interventions to achieve the UNAIDS incidence goal by 2030.
**Methods:** A previously published stochastic, dynamic mathematical model was used to simulate HIV transmission among MSM1. The population was stratified by risk behaviours according to the Greek EMIS study (high=15.1%/ medium=28.7%/low=56.2%). The model was calibrated to match the trajectories of the Greek HIV CoC in the years 2013, 2016, 2019, and 2020. The infection rate, the probability of being diagnosed, and the probability of ART initiation were varied until the model reproduced the observed HIV epidemic of Greece. We examined the effect of the status quo scenario and the HIV elimination scenario.
**Results:** The model showed that although the MSM PLHIV could reach the 95-95-95 target in 2030, this would not be enough to achieve the 90% reduction in HIV incidence (estimated reduction of 32.4% in 2030 compared to 2010). Launching a PrEP intervention only for the high-risk MSM, without any other interventions, would cause a modest incidence reduction (58% in 2030 compared to 2010). To achieve HIV elimination in 2030, the 95-95-95 target should be achieved, all high-risk MSM should be on PrEP, and primary prevention (eg, full condom use) among medium-risk MSM with the target to be moved from medium to low-risk should be implemented (Figure).
**Conclusion:** Reaching the 95-95-95 CoC targets among MSM in Greece is not enough. To achieve HIV elimination, PrEP delivery to high-risk MSM, and primary preventions among medium-risk MSM should be implemented.

## 798 URBAN VERSUS RURAL ACHIEVEMENTS OF 90:90:90 TARGETS IN 12 AFRICAN COUNTRIES

**Suhani Patel**[1], Mansoor Farahani[1], Rachel Bray[1], Jessica E. Justman[1], Wafaa M. El-Sadr[1]
[1]*Columbia University, New York, NY, USA*

**Background:** The relationship between the HIV epidemic and urbanicity is complex, and the HIV urban-rural characteristics are not fully understood. Using the data from Population-based HIV Impact Assessment (PHIA) surveys conducted by ministries of health in collaboration with ICAP and CDC (2015-2019), we compared the HIV epidemic characteristics and the progress toward the UNAIDS 90-90-90 targets in urban vs. rural populations.
**Methods:** Consenting adults from randomly selected households in 12 African countries provided demographic data and blood samples for HIV testing. Estimates of awareness (1st 90) and on-treatment status (2nd 90) were based on self-report or antiretroviral (ARV) detection in blood. Viral load suppression (VLS), the 3rd 90, was defined as HIV RNA <1000 copies/ml. We applied multilevel logistic regression models using survey weights. Variances were estimated using survey-weighted Rao-Scott Chi-Square tests with jackknife variance (Figure).
**Results:** HIV prevalence was significantly higher in urban vs. rural areas in six countries, namely, Cote d'Ivoire, Malawi, Rwanda, Tanzania, Uganda, Zambia. Namibia was the only country where the HIV prevalence was significantly higher in rural than in urban areas. The difference between HIV prevalence in urban and rural areas was not statistically significant In Cameroon, Eswatini, Lesotho, Zimbabwe. In Eswatini, Malawi, and Namibia, the proportion of adults living with HIV (ALWH) aware of their HIV status is higher in the rural areas (88.6% [95%CI 87.2%-90.0%], 78.1% [95% CI 75.3%-80.8%], 88.6% [95% CI 86.5%-90.8%]), compared to urban areas (83.2% [95%CI 80.3%-86.0%], 73.5% [95% CI 70.3%-76.8%], 83.3% [95% CI 79.6%-86.9%]), respectively. In contrast, in Tanzania and Zambia, the proportion of ALWH aware of their HIV status is higher in the urban areas (64.2% [95% CI 60.0%-68.4%], 75.0% [95% CI 72.4%-77.7%]) compared to rural areas (57.6% [95% CI 52.4%-62.7%], 66.2% [95% CI 62.3%-70.2%]). Despite variations in HIV prevalence and knowledge of HIV status between urban and rural areas, we found no significant differences between rural and urban areas in antiretroviral uptake and viral suppression.
**Conclusion:** The findings from these countries with generalized epidemics should guide where HIV testing services should be prioritized to enhance awareness of HIV+ status, a critical first step in the HIV care and treatment cascade.

## 799 AWARENESS OF HIV STATUS AMONG ADULTS LIVING WITH HIV IN 12 AFRICAN COUNTRIES

**Ling Guo**[1], Mansoor Farahani[2], Jessica E. Justman[2], Wafaa M. El-Sadr[2]
[1]*Columbia University, New York, NY, USA,* [2]*ICAP at Columbia University, New York, NY, USA*

**Background:** Awareness of HIV-positive status is critical to contain the epidemic. We assessed characteristics associated with HIV awareness in adults living with HIV (ALWH) (15-59 years) and reasons for not getting tested, using Population-based WHIV Impact Assessment (PHIA) surveys conducted by ministries of health of each country in collaboration with ICAP and CDC.
**Methods:** Consenting adults from randomly selected households in 12 African countries provided demographic and behavioral information and blood samples for HIV testing (Table). We applied multivariable Poisson regression with robust error variance. Variances were estimated via the Jackknife series.
**Results:** Among 239,678 adults, 15,579 (6.5%) were ALWH. Percent awareness of HIV infection ranged from 50.2% in Cote d'Ivoire to 86.8% in Eswatini. Multivariable regression results indicated that men overall and young men and women aged 15-24 years old were less likely to be aware of their HIV-positive status across all countries. Percent of unaware ALWH who had ever tested for HIV ranged from 46.7% (95% CI: 36.7%-56.7%) in Cote d'Ivoire to 81.7% (95% CI: 78.0%-85.4%) in Lesotho. Male sex, younger age, rural residence, and lower education level were associated with lower HIV testing prevalence. Among the subset who tested previously, no more than half (ranging from 21%, in Cote d'Ivoire to 51%, in Eswatini) had tested in the 12 months prior to the survey.
**Conclusion:** In a large randomly selected cohort of ALWH, a substantial percent in several African countries were unaware of HIV infection, particularly men and young adults. Low frequency of recent testing was noted, with data supporting the need for focused and ongoing testing services for youth, males, those with lower educational achievement, and those living in rural areas.

Table 1. Adjusted Odds Ratio of Awareness of HIV Status by sex and age

| | Cameroon | Cote d'Ivoire | Eswatini | Ethiopia | Lesotho | Malawi |
|---|---|---|---|---|---|---|
| **Female (ref)** | - | - | - | - | - | - |
| **Male** | 0.63** (0.46-0.86) | 0.57 (0.3-1.06) | 0.29*** (0.22-0.39) | 0.43** (0.25-0.74) | 0.51*** (0.41-0.63) | 0.54*** (0.41-0.70) |
| **Age groups** | | | | | | |
| **15-24 y/o (ref)** | - | - | - | - | - | - |
| **25-34 y/o** | 3.63*** (2.05-6.42) | 2.12 (0.61-7.37) | 2.37*** (1.57-3.58) | 2.05 (0.90-4.64) | 1.47** (1.08-1.99) | 2.34*** (1.58-3.45) |
| **35-59 y/o** | 7.92*** (4.39-14.3) | 3.07 (0.94-10.01) | 4.90*** (3.36-7.16) | 2.81* (1.08-6.35) | 3.82*** (2.74-5.31) | 4.82*** (3.13-7.42) |
| | | | | | | |
| | Namibia | Rwanda | Tanzania | Uganda | Zambia | Zimbabwe |
| **Female (ref)** | - | - | - | - | - | - |
| **Male** | 0.38** (0.28-0.52) | 0.52** (0.35-0.79) | 0.53*** (0.40-0.71) | 0.47*** (0.36-0.62) | 0.56*** (0.44-0.70) | 0.54*** (0.44-0.65) |
| **Age groups** | | | | | | |
| **15-24 y/o (ref)** | - | - | - | - | - | - |
| **25-34 y/o** | 1.40*** (0.90-2.17) | 1.29 (0.67-2.47) | 1.08 (0.65-1.81) | 2.57*** (1.80-3.66) | 2.08*** (1.53-2.84) | 1.58** (1.16-2.15) |
| **35-59 y/o** | 4.23*** (2.73-6.55) | 3.68*** (1.99-6.78) | 2.39** (1.38-3.51) | 6.28*** (4.41-8.94) | 4.51*** (3.29-6.17) | 3.76*** (2.70-5.06) |

The regression model also included the following variables (not shown here): Urban/rural, marital status, education level and wealth quintile
*: p-value <0.05; **: p-value<0.01; ***: p-value<0.001

## 800 DISCORDANT COUPLES' KNOWLEDGE AND DISCLOSURE OF HIV STATUS IN 10 AFRICAN COUNTRIES

**Mahad Magan**[1], Mansoor Farahani[2], Rachel Bray[2], Domonique M. Reed[1], Jessica E. Justman[2], Wafaa M. El-Sadr[2]
[1]*Columbia University Medical Center, New York, NY, USA,* [2]*ICAP at Columbia University, New York, NY, USA*

**Background:** HIV discordant couples are at the highest risk of HIV transmission and acquisition. A major obstacle in preventing HIV transmission among discordant couples is disclosing their status or knowledge of a partner's status. We examined the association between the demographic characteristics of discordant couples and their disclosure or knowledge of their partner's status, using Population-based HIV Impact Assessment (PHIA) surveys conducted (2015-2019) by ministries of health in collaboration with ICAP and CDC.
**Methods:** Consenting adults from randomly selected households in 10 African countries provided demographic and behavioral information and blood samples for HIV testing (Table). We applied multivariable logistic regression using survey weights. Variances were estimated via Taylor series linearization.
**Results:** A total of 2,352 HIV discordant couples were identified. Compared to men, fewer women reported knowing their partner's status (HIV- or HIV+) in

most countries, ranging from 4% fewer in Rwanda to 12% fewer (75% of males vs. 63% of females) in Malawi, and more women reported having disclosed their status to their partner, ranging from 4% more in Uganda to 17% more in Malawi. Fewer younger discordant couples (15-29 years) knew their partner's status compared to older couples (30-44 years), ranging from 8% fewer in Malawi to 21% (43% of 15-29 years vs. 22% of 30-44 years) in Zimbabwe, and fewer younger couples (15-29 year) disclosed their status to their partner, ranging from 9% fewer who disclosed in Zambia to 18% fewer in Cameroon. Adjusted for other demographic characteristics, women were less likely to know their partner's HIV status (adjusted odds ratio (AOR): 0.8; 95% CI: 0.7-0.9) and more likely to disclose their status to their partner (AOR: 1.8; 95% CI: 1.6-2.0). Age-disparate partners, urbanicity, and economic status were not associated with HIV disclosure.

**Conclusion:** The findings from these nationally representative general population surveys indicate that lack of knowledge of partner's HIV status among discordant couples is common. This lack of knowledge puts women, especially younger women, at risk for HIV acquisition. Efforts are needed to support disclosure during HIV counseling and in an ongoing manner throughout follow-up.

Table 1 Logistic regression models to identify factors associated with HIV status knowledge and disclosure in discordant couples in Cameroon, Eswatini, Lesotho, Malawi, Namibia, Rwanda, Tanzania, Uganda, Zambia, Zimbabwe

| | Knows HIV status of the partner (aOR) | 95% CI | Disclosed HIV status of the partner (aOR) | 95% CI |
|---|---|---|---|---|
| Male (reference group) | - | | - | |
| Female | 0.8†† | (0.7-0.9) | 1.8†† | (1.6-2.0) |
| Age 15-29 years (reference) | - | | - | |
| Age 30-44 years | 1.2†† | (1.1-1.4) | 1.2† | (1.0-1.4) |
| Age 45-59 years | 1.2 | (1.0-1.5) | 1.3†† | (1.1-1.7) |
| Partner Age Gap < 10 Years (reference) | - | | - | |
| Partner Age Gap ≥10 Years | 1.0 | (0.9-1.2) | 0.9 | (0.7-1.1) |
| In Union (reference) | - | | - | |
| Not in Union | 0.4†† | (0.3-0.7) | 0.5†† | (0.3-0.7) |
| Education Level | | | | |
| Education Level Below Secondary (reference) | - | | - | |
| Education Level Secondary & Above | 1.4†† | (1.2-1.6) | 1.4†† | (1.2-1.6) |
| Urban (reference) | - | | - | |
| Rural | 1.1 | (0.9-1.3) | 1.5†† | (1.2-1.8) |
| Wealth index > 40 percentile (reference) | - | | - | |
| Wealth index ≤ 40 percentile | 0.9 | (0.7-1.0) | 0.8†† | (0.6-0.9) |

p < 0.01 ††; p < 0.05 †
Country level fixed effect included in the model, not shown here

## 801 DIVERSE TIME TRENDS IN SEXUAL BEHAVIOR AFTER HIV DIAGNOSIS OVER 20 YEARS FOLLOW-UP

**Kalongo Hamusonde**[1], Dunja Nicca[2], Huldrych F. Günthard[3], Marcel Stöckle[4], Katharine E. Darling[5], Alexandra L. Calmy[6], Roger Kouyos[3], Andri Rauch[1], Luisa Salazar-Vizcaya[1]
*[1]University Hospital of Bern, Bern, Switzerland, [2]University of Basel, Basel, Switzerland, [3]University Hospital Zurich, Zurich, Switzerland, [4]University Hospital Basel, Basel, Switzerland, [5]University of Lausanne, Lausanne, Switzerland, [6]University of Geneva, Geneva, Switzerland*

**Background:** To characterize sexual behavioral heterogeneity among persons recently diagnosed with HIV and sexual behavioral changes thereafter, we used unsupervised and supervised machine learning algorithms on 20 years of baseline and follow-up data from the Swiss HIV Cohort Study (SHCS). We sought to identify behavioral clusters near diagnosis and to assess long-term time trends in changes in sexual behavior across them. We then compared these trends between men who have sex with men (MSM) and heterosexual (HET) persons living with HIV (PLWH).

**Methods:** Hierarchical principal component analysis inferred sexual behavior clusters based on combinations of variables on sexual behavior, non-sex related behavior and socio-demographics at baseline. A random forest classifier evaluated the role of these factors in cluster formation. We then assessed cluster specific time-trends in the search for differences between MSM and HET.

**Results:** Analyses included 3,903 PLWH registered in the SHCS between 1999 and 2021 less than 6 months after HIV diagnosis who identified themselves as MSM (n=1,839) or HET (n=2,064). At registration, 44% of MSM and 56% of HET reported stable partnership while 78% MSM and 22% HET reported occasional partnership without significant changes during 20 years of follow-up. Overall, consistent condom use decreased considerably in both MSM and HET with stable partner (60% to 25% in MSM and 63 to 25% in HET; Figure 1A). Consistent condom use with occasional partner also declined for both (70% to 38% in MSM and 83% to 50% in HET). Our clustering algorithm identified 5 distinct behavioral clusters (C1-C5; Figure 1B). Sex with stable partner, condom use with stable partner and HIV status of stable partner where the most important features for this cluster formation. Trajectories of consistent condom use during follow-up with stable partner differed among clusters but were similar between MSM and HET except for clusters C1 and C4 comprising 15% of the study population (Figure 1C).

**Conclusion:** In 20 years of follow-up after HIV diagnosis, MSM and HET PLWH had similar, decreasing trends in condom use with stable and occasional partners. Algorithmically defined behavioral grouping soon after HIV diagnosis was only marginally sensitive to sexual preference. Moreover, differences between MSM and HET in sexual behavior time-trends after HIV-diagnosis other than occasional partnership were limited to a small fraction of the population.

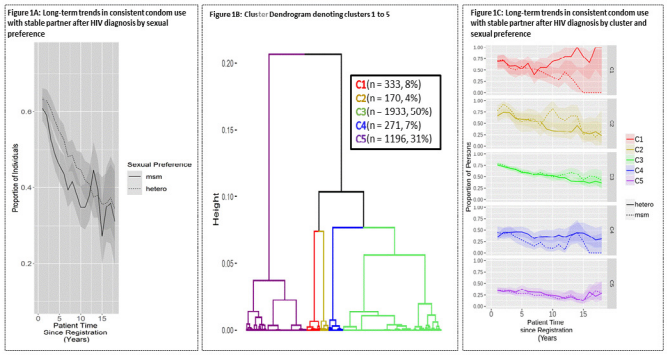



Figure 1A: Proportion of the study population's overall trends of consistent condom use with stable partner during study period (1999 to 2021) after HIV diagnosis between men who have sex with men (msm) and heterosexuals (hetero) in the Swiss HIV Cohort Study (SHCS).
Figure 1B: Dendrogram showing 5 behavioral clusters formed from the following variables: sexual partnership during last 6 months, sexual intercourse (anal or vaginal) with the stable partner, condom use with stable partner, HIV status of stable partner, occasional partners during last 6 months, suffered from depression, alcohol use, injection drug use, cannabis use, ethnicity, center of registration, registration date, age at registration, level of education at registration, sexual orientation (MSM or heterosexual) and sex.
Figure 1C: Proportion of the study population trends from HIV diagnosis and 20 years of follow-up distributed by cluster between men who have sex with men (msm) and heterosexuals (hetero) in the Swiss HIV study cohort.

## 802 AUTHORSHIP INEQUALITIES IN GLOBAL HEALTH RESEARCH INITIATIVE

**Veronika W. Skrivankova**[1], Stefanie Hossmann[1], Carole Dupont[1], Morna Cornell[2], Marie Ballif[1], Matthias Egger[1]
*[1]Institute of Social and Preventive Medicine, Bern, Switzerland, [2]University of Cape Town, Cape Town, South Africa*

**Background:** The International epidemiology Databases to Evaluate AIDS (IeDEA) are a global research consortium of researchers from low-, middle- and high-income countries established in 2006. IeDEA is a highly productive collaboration, having published over 1500 articles. We assessed gender and regional inequalities in publication rates and authorship position among articles produced in 2007-2020 by the Southern Africa region of IeDEA (IeDEA-SA), led by the University of Cape Town, South Africa, and the University of Bern, Switzerland.

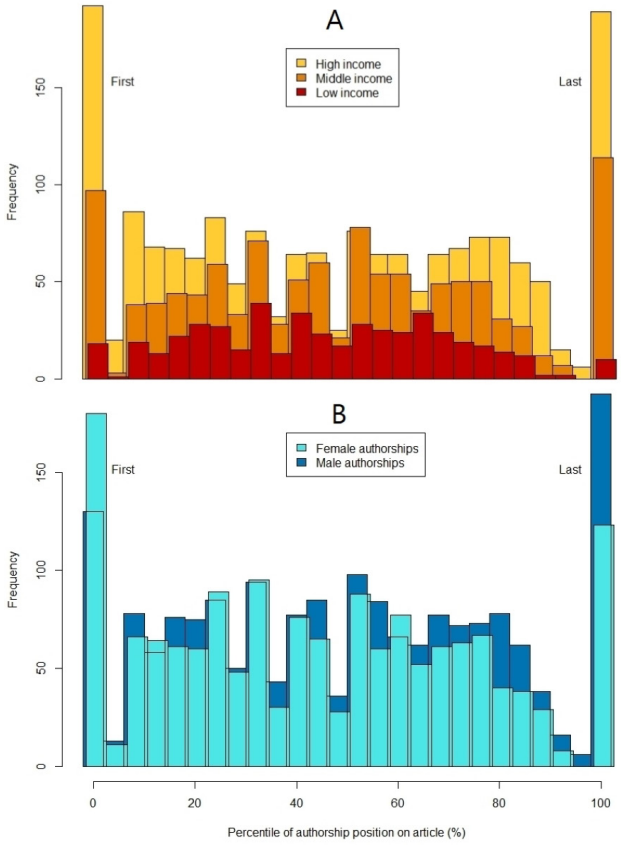
**Methods:** We extracted authors' names and affiliations from 313 published articles acknowledging IeDEA-SA funding, excluding articles with groups listed as authors. We assigned income levels of the authors' country as indicated in their primary affiliations using the World Bank's classification. We determined the authors' gender based on their first names using the US Social Security and Census databases. We recovered missing values by contacting corresponding authors by email. We compared distributions of authorship positions by country income level and gender. We assessed differences in authorship position (first and last author versus central authorship) by gender and country income level using generalized multinomial regression model with random intercept for authors.

**Results:** Among 1086 contributing authors, 219 (20%) were from low-income countries (LIC), 269 (24%) from middle-, 565 (52%) from high-income countries (HIC), and 558 (51%) were female. During their time in IeDEA-SA between 2007 and 2020, LIC authors published on average 2.3 articles, compared to 3.1 articles

for authors from HIC. Moreover, LIC authors were less likely to publish as either first or last author compared to HIC authors (Fig 1A), with the corresponding odds ratios OR=0.23 (0.12-0.46) and OR=0.20 (0.10-0.44), respectively. Female authors published on average 2.8 articles, compared to 3.5 articles published by male authors. While women were more likely to publish as first authors than men, OR=1.67 (1.03-2.72), they were less likely to publish as last authors, OR=0.64 (0.41-0.99) (Fig 1B).

**Conclusion:** In our study, authors from LIC published less than authors from HIC and were under-represented at both first and last authorship positions. Female authors published less than male authors and were under-represented at the last authorship position, while they were over-represented at the first position. Monitoring of publication rates and authorship position promotes transparency and equity.

Figure 1: Distribution of authorship positions by A) income level of author's country of affiliation and B) author's gender. The authorship positions within an article are converted to percentiles (standardized). First authorship corresponds to 0-th percentile, last authorship corresponds to 100-th percentile.




## 803 ANALYSIS OF RECENT INFECTION AMONG PERSONS NEWLY DIAGNOSED WITH HIV IN NIGERIA

**Moses Katbi**[1], Adefisayo Adedoyin[2], Amobi Onovo[1], Adeoye Adegboye[1], Rachel Goldstein[1], Helina Meri[1], Angela Agweye[1], Pamela Gado[1], Amalachukwu Ukaere[1], David Onime[1]

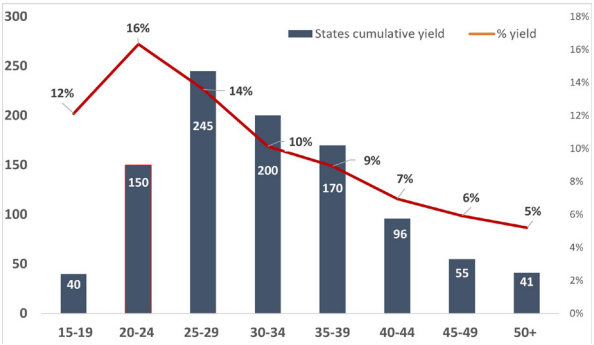
[1]*United States Agency for International Development, Abuja, Nigeria,* [2]*Society for Family Health, Abuja, Nigeria*

**Background:** Understanding the dynamics of recent infection among people newly diagnosed with HIV may help in identifying geographic areas and subpopulation with high HIV transmission rates for super targeted testing. Recency testing helps to detect people who were recently infected with HIV so that prevention programs can focus on preventing incident infections to reduce new infection rate and ultimately interrupt further transmission to achieve epidemic control. The PEPFAR team in Nigeria introduced recency testing in 2020. We analyzed recent infection among newly diagnosed PLHIV in 10 states.

**Methods:** Testing for recent infection using pre-approved recency test kit was conducted for newly diagnosed HIV positive clients in 10 states over an 18-month period. Using One way Welch ANOVA we determined if there was any difference in the recent infection yields of different age groups. Welch T- test was done to determine if any significant difference exist in the recency testing yield between male and female. We carried out a Multinomial regression to determine how well gender and age range can predict recency yield in the states

**Results:** A total of 10,070 PLHIV (male=40%; female=60%) where tested for recent infection with 10% (n=1010; (male=39%; female=61%) identified as having recent HIV infection. One-way Welch ANOVA shows statistically significant difference in recency testing yield for the 8 different age groups, Welch's F (7, 304.463) = 183.574, p<0.0005., the highest yield for recent infection was seen in the age group 20-24 years (16%) while the lowest in the age group 50+ (4%). Females generally had higher recent infection rates (11%) than men (9%). Games-Howell post hoc analysis revealed that the difference in the mean for the age groups with the highest (25-29 years) and lowest (15-19 years) number of recent infections was significant. Welch T test shows that the difference in the mean yield between male and female was statistically significant with a mean difference of 131. 624 (95%CI = -144.635 to -118.613); t (873.43) = 19.855; p < 0005. Multinomial regression shows a statistically significant likelihood ratio test for both gender and age range. This means that gender and age significantly improve yield prediction in the sates.

**Conclusion:** Recent infection is higher among certain age group and varies across states. Recent infection rate is higher among females. HIV intervention should be prioritized to focus on the age range and sex with the highest new infection rates by geography.




## 804 EVALUATION OF HIV-1 RECENCY ASSAYS AMONG PROSPECTIVELY OBSERVED HIV-1 SEROCONVERSIONS

**Stephanie Cox**[1], Christoph Carter[1], Alex Kintu[1], Christian Callebaut[1], Jared Baeten[1], Moupali Das[1]

[1]*Gilead Sciences, Inc, Foster City, CA, USA*

**Background:** HIV-1 recent infection testing algorithms using recency assays have been successfully used to determine population-level HIV-1 incidence rates and are currently being employed to determine background HIV incidence rates in several Phase III PrEP trials. To better understand the performance of recency assays in the context of a PrEP trial, we applied 3 different recency assays to well-documented seroconversion samples from the DISCOVER study, a large Phase III study of F/TAF versus F/TDF for PrEP.

**Methods:** Forty-two uniquely dated plasma samples from 25 participants who acquired HIV-1 during the DISCOVER trial were tested with the Sedia HIV-1 Limiting Antigen Avidity EIA (LAg-EIA; Sedia Biosciences, Beaverton, OR), the Sedia Asante HIV-1 Rapid Recency Assay (Asante; Sedia Biosciences) and the Abbott ARCHITECT Assay (ARCHITECT; LabCorp, Indianapolis, IN). Out of the 42 samples, 3 samples were available for testing by 2 out of the 3 assays while 1 sample was tested by only 1 assay. Thirty-three samples were recent (<6 months since estimated date of HIV-1 acquisition during prospective follow-up) and 10 were long-term (>6 months). The determination of recent or long-term infection was based on the assay specific immunoassay threshold and mean duration of recent infection (MDRI), which was the average time post-infection that individuals were classified as recently infected.

**Results:** Samples were predominantly subtype B (22/25 participants). The LAg-EIA assay correctly classified 93% as recent or long-term (see Table). The Asante assay classified 84% and the ARCHITECT assay classified 88% correctly. Out of the incorrectly called samples, the Asante assay classified 2 long-term samples as recent, the LAg-EIA called 1 of the same long-term samples as recent, while the ARCHITECT did not classify any long-term infections as recent. In the samples that were misclassified as long-term, 3 were incorrectly called by all 3 assays with an additional 2 samples incorrectly called by 2 out of 3 assays, suggesting a sample specific attribute.

**Conclusion:** The LAg-EIA, Asante, and ARCHITECT assays were able to discriminate between recent and long-term infections seen in the DISCOVER study. All 3 assays identified the recent infections with a similarly high degree of accuracy. Overall, these analyses support the use of these laboratory assays in determining the bHIV-IR in future PrEP trials.

| Assay | # of samples tested | # called correctly (%) | # called incorrectly (%) | Recent called Long-term | FRR (Long-term called Recent) |
|---|---|---|---|---|---|
| ARCHITECT | 40 | 35 (87.5) | 5 (12.5) | 5 | 0 |
| Asante | 38 | 32 (84.2) | 6 (16) | 4 | 2 |
| LAg-EIA | 41 | 38 (92.7) | 3 (7) | 2 | 1 |

## 805 NEAR-UNIVERSAL COVERAGE OF RECENT HIV TESTING IN RURAL UGANDA: POPULATION-BASED STUDY

**Holly Nishimura**[1], Ruth Young[2], Joseph G. Rosen[2], Nora S. West[1], Joseph Ssekasanvu[1], Robert Ssekubugu[3], Fred Nalugoda[3], Gertrude F. Nakigozi[3], Steven J. Reynolds[4], Larry W. Chang[5], David Sserwadda[3], Joseph Kagaayi[3], M. Kate Grabowski[5]

*[1]The Johns Hopkins University, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]Rakai Health Sciences Program, Kalisizo, Uganda, [4]US National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [5]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** Frequent HIV testing is necessary to identify individuals with incident HIV infection and rapidly enroll them into HIV care and treatment. However, most studies in sub-Saharan Africa measure prevalence of lifetime HIV testing, rather than ascertaining when individuals were last tested. Here, we assessed prevalence and correlates of past-year HIV testing in a population-based study in south-central Uganda.

**Methods:** This analysis used a single round of survey data from the Rakai Community Cohort Study (RCCS) collected between 2016-18. The analytic sample was restricted to first-time RCCS participants aged 15-49 who were sexually active (N=2,830). Recent HIV testing was defined as testing in the past 12 months. Putative demographic and behavioral correlates of recent testing were identified a priori and assessed for association with past-year HIV testing using multivariable Poisson regression with robust standard errors, stratified by gender. Measures of association were reported as adjusted prevalence ratios (aPR) with 95% confidence intervals (CI).

**Results:** A majority (77.9%) of participants reported HIV testing in the last 12 months, with a significantly higher proportion in those aged 15-24 (82.3% vs. 72.8% 25+ years, p<0.001) and in women (83.7% vs. 70.1% men, p<0.001). Among non-recent testers (n=626), 73.3% had tested in the last 2 years. Key and priority populations (KP) (i.e., boda boda drivers, female sex workers and their clients, fisherfolk) comprised 37.6% of the sample (n=1063). Among KP, women had higher rates of past-year testing relative to men (86.6% vs. 74.1%, p<0.001). In multivariable analysis, correlates of recent testing among men included secondary or higher educational attainment (aPR=1.15, CI:1.05–1.25) and, for women, inconsistent condom use with casual partners (aPR=1.14, CI:1.02–1.28).

**Conclusion:** High rates of past-year HIV testing, particularly among adolescent girls and young women, in this rural population-based sample, suggest universal testing targets are within reach. Additional outreach efforts, through differentiated testing modalities (i.e., self-testing, community-based approaches), could support targeted testing services to reach men, in particular.

## 806 HIGH POSITIVITY AMONG CLIENTS OF A VIRTUAL HIV TESTING STRATEGY IN INDIA

**Jade Bell**[1], Allison M. McFall[2], Jalpa H. Thakker[1], Ajay K. Enugu[1], Viswanathan Arumugam[3], Rose Pollard[1], Vikrant Gupta[3], Aditya Singh[1], Samit Tandon[4], Harsh Agarwal[3], Aylur K. Srikrishnan[3], Subash Ghosh[3], Shruti H. Mehta[2], Sunil S. Solomon[1], Sangeeta Kaul[5]

*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]YR Gaitonde Center for AIDS Research and Education, Chennai, India, [4]Blue Lotus Advisory, Delhi, India, [5]US Agency for International Development, Delhi, India*

**Background:** Globally, populations at risk continue to evolve, but HIV testing approaches have remained largely stagnant. Specifically, penetration of the internet and anonymity of online 'hook-up' platforms have led clients to seek partners in virtual vs. physical spaces; these individuals are not reached by traditional HIV testing approaches. We present findings from a virtual outreach program for education and HIV service linkage.

**Methods:** We established a team of virtual outreach workers (vORW) who reached potential clients via online dating (eg, Grindr) and social media platforms. They chatted with clients, promoted safe sex practices and assisted in booking an HIV test via an online testing platform. Clients had to be ≥ 18 years old and complete a risk assessment before booking a test at a physical site. vORWs assisted clients testing positive with confirmatory testing and ART linkage. Process measures across the testing continuum were captured. Correlates of a positive screening test were explored using logistic regression.

**Results:** From Oct 2019-Sep 2021, 9,355 HIV testing reservations were made across 22 Indian states. Median age was 29; 94% were male, 4% female and 2% transgender. Most (83%) identified as men who have sex with men (MSM). Three quarters of clients reported no prior HIV test. In the last 6 months, 85% reported condomless sex, 44% multiple sex partners and 12% substance use before sex. Of 9,355 reservations, 6,839 (73%) screening tests were completed and 491 (7%) screened HIV positive of whom only 27% had previously been tested (Figure). Positivity varied by region (2% in West to 8% in North). Among those who screened positive, 76% had confirmatory testing, of whom 99% were confirmed positive and 69% initiated ART. Those with no prior HIV test were less likely to get a confirmatory test and initiate ART. Factors significantly associated with a positive screening test were being male (aOR 3.02), reporting sex with men/women only (no transgender partners) (aOR 1.62), recent needle sharing (aOR 3.63) and positive syphilis test (aOR 2.78).

**Conclusion:** These results highlight the feasibility and effectiveness of a vORW approach coupled with an online testing platform to reach a high-risk population, the vast majority of whom had not been reached by traditional HIV programming. Additional effort may be needed to link those new to HIV services to ART and move closer to 95-95-95 targets.

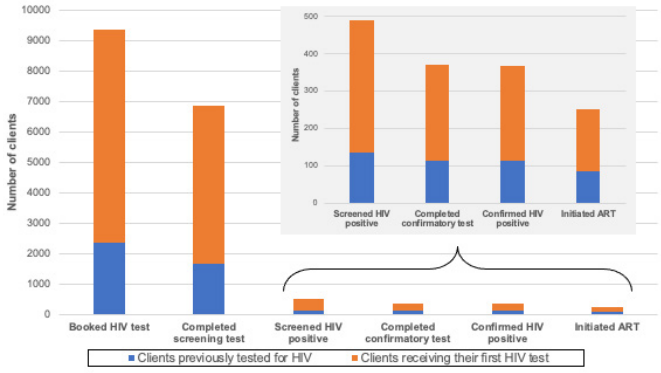



**Figure. HIV testing cascade among 9,355 clients reached by a virtual testing platform across 22 states in India (October 2021-September 2022).**

## 807 FACEBOOK ADVERTISEMENTS COST PER NEW HIV DIAGNOSIS USING ROUTINE AND TARGETED MODELS

**John Hanna**[1], Ank Nijhawan[1], Christoph U. Lehmann[1], Richard Medford[1]

*[1]University of Texas Southwestern, Dallas, TX, USA*

**Background:** Undiagnosed Human immunodeficiency virus (HIV) infection continues to be a public health challenge. Previous studies used the Facebook (FB) advertisements (Ads) platform to recruit HIV populations at risk. In this study, we explore FB Ads cost per new HIV diagnosis using non-targeted Ads and routine testing model against targeted FB Ads and focused testing model in the state of Texas.

**Methods:** On 10/14/2021, we created (without actually launching) 10-day Texas-based $10 targeted (using criteria matching HIV populations at risk; Men with interests on FB that included LGBT culture, LGBT community, homosexuality, same-sex marriage, and same-sex relationship) and non-targeted FB Ads for different age groups in Texas counties with high HIV prevalence rates. We collected FB provided parameters such as estimated audience size, estimated daily reach, and estimated daily clicks per Ad. We then estimated average Ads cost per new HIV diagnosis for targeted and non-targeted Ads using new HIV diagnosis rates from focused testing and routine testing campaigns in Texas.

**Results:** Cost per new HIV diagnosis of targeted FB Ads was 4.74, 2.86, and 5.28 times lower among men, Black and Hispanic individuals respectively when compared to non-targeted Ads. Among all age groups, targeted ads and focused testing approach cost was on average 2.88 times lower than non-targeted Ads and routine testing approach. Cost varied based on FB Ads' cost and new HIV

diagnosis rates for each targeted population. The wider the gap was between focused and routine testing's new HIV diagnosis rates in a population, such as in Ft. Worth and Houston, the more cost-effective targeted Ads became compared to non-targeted Ads.

**Conclusion:** Targeted FB Ads are more cost-effective than non-targeted Ads among HIV populations at risk, across all age groups and in locations for which focused testing yields substantially higher new HIV diagnosis rates compared to routine testing. Our study results can guide public health agencies and local communities in optimizing resources to address the HIV epidemic, as social media Ad strategies are useful for improving HIV prevention, testing, and treatment.

| | Targeted Ads and Focused Testing | | | Non-Targeted Ads and Routine Testing | | |
|---|---|---|---|---|---|---|
| | new diagnosis rate | Average estimated audience size on Facebook | Average Cost per new HIV diagnosis | new diagnosis rate | Average estimated audience size on Facebook | Average Cost per new HIV diagnosis |
| Men | 1.0% | 1,350,000 | $33.06 | 0.2% | 11,050,000 | $156.74 |
| Black | 0.8% | 289,550 | $64.94 | 0.2% | 2,100,000 | $185.53 |
| Hispanic | 0.8% | 784,300 | $73.31 | 0.1% | 3,050,000 | $386.85 |
| 18-24 | 0.8% | 326,450 | $113.64 | 0.1% | 4,800,000 | $534.76 |
| 25-34 | 0.9% | 483,300 | $91.83 | 0.2% | 6,900,000 | $181.82 |
| 35-44 | 0.8% | 236,250 | $103.31 | 0.1% | 4,900,000 | $371.06 |
| 45-54 | 0.6% | 125,000 | $144.30 | 0.1% | 3,400,000 | $363.64 |
| 55-64 | 0.3% | 76,700 | $224.47 | 0.1% | 2,350,000 | $356.51 |
| 65+ | 0.2% | 60,000 | $413.22 | 0.0% | 2,050,000 | |
| Austin | 0.4% | 110,100 | $206.61 | 0.1% | 1,750,000 | $443.46 |
| Dallas | 1.0% | 264,700 | $86.58 | 0.3% | 4,650,000 | $114.35 |
| Fort Worth | 0.9% | 162,000 | $91.83 | 0.1% | 3,100,000 | $371.06 |
| Houston | 0.7% | 288,500 | $123.69 | 0.1% | 4,750,000 | $404.04 |
| San Antonio | 0.6% | 121,400 | $168.35 | | 2,050,000 | |
| Rest of Texas | 0.8% | 189,150 | $126.26 | 0.1% | 9,700,000 | $356.51 |

## 808 INTEGRATION OF HIV AND HCV SERVICES WITH MEDICATION FOR OPIOID USE DISORDER IN THE US

**Eshan U. Patel**[1], Becky L. Genberg[1], Xianming Zhu[2], Noa Krawczyk[3], Shruti H. Mehta[1], Aaron Tobian[2]

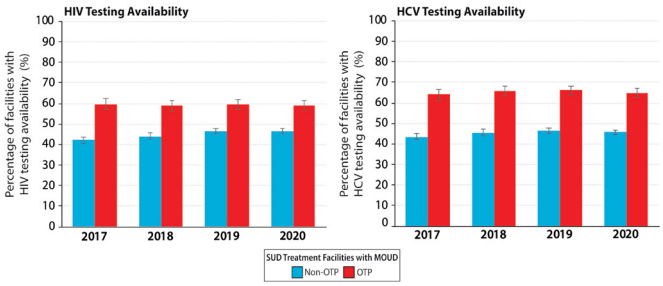
*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3]New York University, New York City, NY, USA*

**Background:** The US National Strategic Plan to End the HIV Epidemic (EHE) includes recommendations to integrate programs combatting the syndemics of HIV, viral hepatitis, and substance use disorders (SUDs). Facilities that offer medication for opioid use disorder (MOUD) are ideal settings to co-locate HIV/HCV services, as they serve a high-risk population and MOUD is associated with improved HIV/HCV treatment outcomes. We examined HIV/HCV testing and treatment availability in SUD treatment facilities that offer MOUD in the US.

**Methods:** The 2017-2020 National Survey of Substance Abuse Treatment Services is an annual census of US SUD treatment facilities (response rates=89-92%). The analysis was restricted to facilities that offer MOUD (methadone/buprenorphine/naltrexone) and stratified by federal Opioid Treatment Program (OTP) status, with non-OTPs being facilities that only offer buprenorphine/naltrexone. Prevalence differences (PD) in HIV/HCV testing availability between 2017 and 2020 were examined using binomial regression. We also assessed HIV/HCV testing and treatment availability by facility factors in 2020.

**Results:** Between 2017 and 2020, the no. of facilities that offered MOUD increased from 5143 to 8250 and the no. of OTPs increased from 1317 to 1754. Over this period, HIV testing availability only increased from 42.2% to 46.6% in non-OTPs (PD=4.4 [95%CI=2.4, 6.3) and there was no change among OTPs (59.7% to 59.0%; PD=-0.7 [95%CI=-0.4, 2.8]). HCV testing availability only increased from 43.5% to 45.8% in non-OTPs (PD=2.3 [95%CI= 0.4, 4.3]) and there was no change among OTPs (64.1% to 65.0%; PD=0.9 [95%CI=-2.5, 4.3]). Of the non-OTPs in 2020, 17.9% (n=1,163) offered HIV treatment and 20.5% (n=1,334) offered HCV treatment. Of the OTPs in 2020, 8.9% (n=156) offered HIV treatment and 10.7% (n=188) offered HCV treatment. Regardless of OTP status, private for-profit facilities were less likely than federal facilities to offer HIV/HCV testing and treatment services. In the EHE high-priority rural states, less than half of non-OTPs (44.9%; n=279) and OTPs (46.2%; n=54) offered HIV testing, and only 11.3% (n=70) of non-OTPs and 4.3% (n=5) of OTPs offered HIV treatment.

**Conclusion:** Despite increases in the number of facilities providing MOUD in the US, integration of HIV and HCV services remains suboptimal, particularly in EHE high-priority rural states. This represents a missed opportunity to engage at risk marginalized populations in HIV and HCV care, which will be critical for achieving EHE goals.




## 809 PARTNER VIOLENCE, DISTRESS, AND HIV TESTING IN HETEROSEXUALLY ACTIVE ADULTS IN THE US

**Cassandra O. Schember**[1], Susan Cha[2], Meredith R. Brantley[3], Peter F. Rebeiro[1], Samantha A. Mathieson[3], Jack Marr[3], April Pettit[1]

*[1]Vanderbilt University, Nashville, TN, USA, [2]Centers for Disease Control and Prevention, Atlanta, GA, USA, [3]Tennessee Department of Health, Nashville, TN, USA*

**Background:** Persons experiencing intimate partner violence (IPV) are disproportionately vulnerable to HIV. Previous studies have established associations between IPV and increased psychological distress (PD) and decreased HIV testing; PD is also a correlate of decreased HIV testing. We hypothesized that PD may mediate the relationship between IPV and lack of HIV testing, and provide an opportunity to increase HIV testing among heterosexually active adults in the United States (US).

**Methods:** Using multi-site (N=23 US cities) data from the 2019 National HIV Behavioral Surveillance (NHBS) high-risk heterosexual cycle, we assessed the relationship between IPV, and lack of a recent HIV test (prior 12 months) mediated through PD. Participants self-reported IPV (physical or sexual violence) in the past 12 months, severe PD (using Kessler Scale score of ≥13) in the past 4 weeks, and lack of recent HIV test. We estimated adjusted prevalence ratios (aPR) and 95% confidence intervals (CI) using modified Poisson regression with generalized estimating equations clustering by recruitment chain and adjusting for age, gender, US region, network size, race/ethnicity, housing status, educational attainment, marital status, non-injection drug use, binge drinking, and number of opposite-sex partners in the past year. Through mediation analysis, we assessed the natural indirect effect (NIE) for the relationship between IPV and lack of recent HIV test mediated through PD.

**Results:** Among 9,342 heterosexually active adults, 1,912 (20.5%) experienced IPV, 1,581 (16.9%) experienced PD, and 5,582 (59.8%) had not been tested for HIV in the past 12 months. IPV was positively associated with PD and negatively associated with HIV testing history, but PD was not significantly associated with HIV testing history (Table 1). PD was also not a significant mediator in the relationship between IPV and HIV testing, as the NIE was null (aPR: 0.94, 95% CI: 0.93, 1.08).

**Conclusion:** Among the NHBS sample of heterosexually active adults at high risk for HIV, those experiencing IPV were more likely to have experienced PD and less likely to have tested for HIV in the past year. PD was not significantly associated with lack of HIV testing and was not a mediator in the relationship between IPV and HIV testing. Those experiencing IPV should continue being tested for HIV more frequently than those not experiencing IPV, but more attention needs to be given to providing PD care for those experiencing IPV.

**Table 1.** ADJUSTED PREVALENCE RATIOS (aPR) FOR RELATIONSHIPS BETWEEN INTIMATE PARTNER VIOLENCE (IPV), PSYCHOLOGICAL DISTRESS (PD), AND HIV TESTING

| Relationship | aPR* | 95% Confidence Interval |
|---|---|---|
| IPV and HIV Testing | 0.95 | 0.91-0.99 |
| IPV and PD | 1.95 | 1.77-2.14 |
| PD and HIV Testing | 1.04 | 1.00-1.08 |

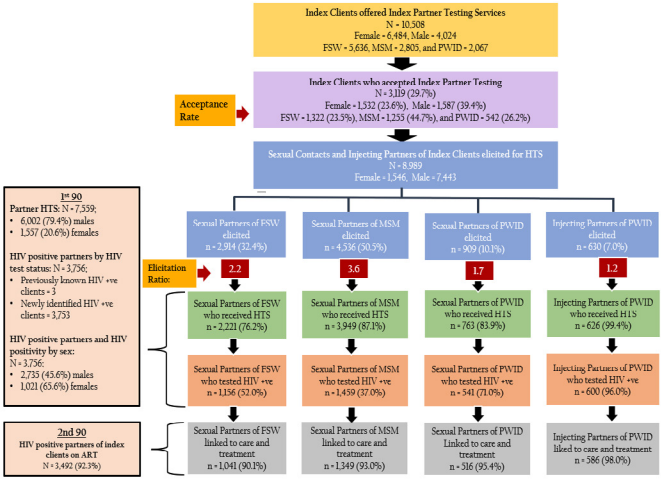
*Assessed using modified Poisson regression with generalized estimating equations clustering by recruitment chain and controlling for age, gender, US region, network size, race, housing status, educational attainment, marital status, non-injection drug use, binge drinking, and number of opposite sex partners in the past year

## 810 HIV DIAGNOSIS AND LINKAGE TO CARE IN PARTNERS OF KEY POPULATION IN NIGERIA

**Amobi Onovo**[1], Kalaiwo Abiye[1], Angela Agweye[1], Godwin Emmanuel[1], Olivia Keiser[2]

*[1]US Agency for International Development Nigeria, Abuja, Nigeria, [2]University of Geneva, Geneva, Switzerland*

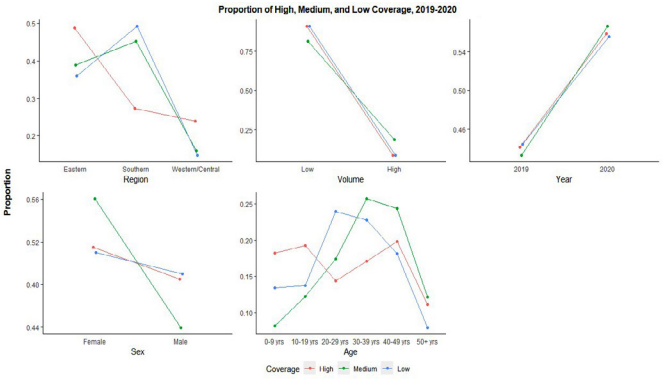
**Background:** The HIV epidemic in Nigeria is concentrated in Key Populations (KP), people who inject drugs (PWID), men who have sex with men (MSM), female sex workers (FSW), and partners of people living with HIV. Due to stigma and discrimination, these groups have low access to HIV testing services (HTS) and linkage to treatment is challenging. To address this gap, index partner testing, targeting sexual contacts and injecting partners of KP index clients, was introduced in 2017.
**Methods:** The study was a retrospective analysis of community-led HIV index partner testing-involving review of secondary data from PNS registers. Between October 1, 2018, and September 30, 2019, HIV testing as part of index partner testing services was offered at nightclubs, hotels, and community-based ART clinics in the states of Akwa Ibom, Cross River, and Lagos. Index testing was assisted by peer navigators. We used provider and passive PN methods. In-person and social network methods were used to recruit partners of KP. We described the implementation of index partner testing services as part of the national KP program, analyzed Partner Notification (PN) delivery models, and calculated HIV seropositivity among persons who underwent Index Partner Testing. One-Way ANOVA and Tukey-HSD test were performed to determine whether the differences in mean HIV seropositivity between partners are statistically significant.
**Results:** PN was predominantly done through provider referral 5,159 (68.3%) and client referral 2,278 (30.1%). A total of 3,119 index partners; 1,322 FSW (42.4%), 1,255 MSM (40.2%) and 542 PWID (17.4%) identified 8,989 sexual and injecting partners (index partner ratio 1:2.9). Among the partners, 7,556 (84.1%) were first-time testers, and 79.4% (5,999) of male partners tested. Of the 3,753 (49.7%) partners tested HIV-positive, 3,492 (93.0%) were enrolled in HIV care. HIV seropositivity rate was 65.5% (1,021/1,557) among females and 45.5% (2,732/5,999) among males and was disproportionately higher among PWID injecting partners 99.1% (581/586), PWID sexual partners 98.9% (433/438) and MSM sexual partners 95.6% (605/633) in Cross river compared with 71.4% (575/805) in FSW sexual partners.
**Conclusion:** Including index partner testing as part of a community-led HTS can help improve HIV case-finding approach for KP, particularly for reaching first-time testers, male KP, and persons not yet diagnosed with HIV. Scale-up of index partner testing within community-led HTS is essential for achieving UNAIDS 95-95-95 goals.




## 811 CHARACTERISTICS OF HEALTH FACILITIES ASSOCIATED WITH LOW HIV VIRAL LOAD COVERAGE

**Fatima D. Mili**[1], Jennifer F. Favaloro[1], Mackenzie Hurlston Cox[1], Shiraishi W. Ray[1], Larry Westerman[1], Amitabh P. Adhikari[1], Jessica Stephens[2], Heather Alexander[1], Erin Rottinghaus Romano[1]
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]United States Agency for International Development, Washington, DC, USA*

**Background:** The 2013 WHO antiretroviral guidelines recommended routine testing of HIV viral load (VL) (concentration of HIV RNA copies/mL of blood) as the preferred method for monitoring treatment in people living with HIV (PLHIV). The 2020 UNAIDS targets proposed that all PLHIV receiving antiretroviral therapy (ART) have access to HIV viral load testing (VLT) as part of public health programs aiming to reduce HIV transmission. In limited-resource countries, PLHIV are facing various challenges to VLT access, and some might be associated with health-related facility factors.
**Methods:** To identify characteristics of facilities associated with low VLT coverage (VLTC)), we analyzed data reported to the Monitoring, Evaluation, and Reporting (MER) System by 17 PEPFAR-supported sub-Saharan African countries in 2019 and 2020. We used ordinal logistic regression model accounting for clustering with assumption of random effect model on facility. Outcome variable was VLTC (proportion of the number of PLHIV with a VL in the medical record or laboratory record/laboratory information system within the past 12 months divided by the number of PLHIV receiving ART six months earlier) categorized as Low (< 70%), Medium (70% to < 90%), and High (>= 90%). Independent variables were region (Eastern, Southern, Western/Central Africa), age (0-9, 10-19, 20-29, 30-39, 40-49, 50+ years), sex (male, female), and volume (low volume: <100 PLHIV on ART vs. high volume: >=100 PLHIV on ART) by facility.
**Results:** The odds of VLTC were higher in the Southern region (adjusted odds ratio [AOR] = 1.95; 95% CI 1.92, 1.97) and lower in the Western/Central region (AOR = 0.86; 95% CI 0.85, 0.88) as compared with Eastern region. The AOR for VLTC was lower for high volume as compared with low volume facilities (AOR = 0.69; 95% CI 0.67, 0.70). The year 2020 had a lower AOR for VLTC (AOR = 0.98; 95% CI 0.97, 0.99) than 2019. Males had an AOR for VLTC of 1.00 compared with females, and as age increased so did AOR for VLTC (AOR = 1.02; 95% CI 1.02, 1.02).
**Conclusion:** Gaps in HIV VL testing coverage have increased since 2019, potentially due to the COVID-19 pandemic. Regional gaps were seen in Western/Central Africa and with increased facility volume. Potential gaps might be seen in younger PLHIV. Identifying barriers to scale-up of HIV VL monitoring in facilities with low volume to develop and implement effective public health strategies could help to improve PLHIV outcomes and accelerate progress toward HIV epidemic control in these regions.



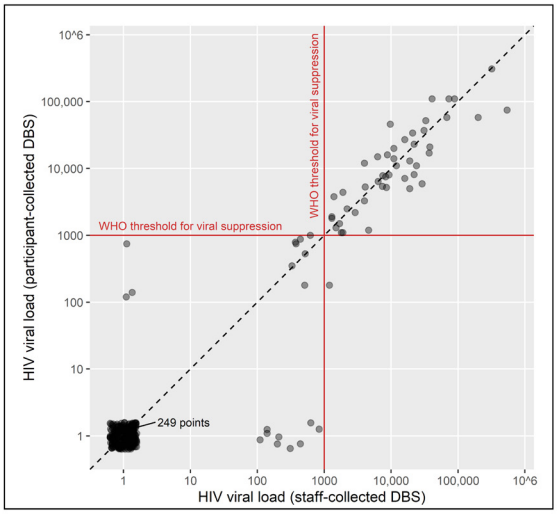

## 812 PATIENT-COLLECTED DRIED BLOOD SPOTS PROVIDE ACCURATE MEASUREMENT OF HIV VIRAL LOAD

**Torin T. Schaafsma**[1], Katherine K. Thomas[1], Heidi Van Rooyen[2], Maryam Shahmanesh[3], Stephen Asiimwe[4], Meighan Krows[1], Philip Joseph[2], Thulani Ngubane[5], Kombi Sausi[5], Nsika Sithole[3], Jared Baeten[1], Connie L. Celum[1], Alastair Van Heerden[6], Ruanne Barnabas[1]
*[1]University of Washington, Seattle, WA, USA, [2]Human Sciences Research Council, Pretoria, South Africa, [3]Africa Health Research Institute, Mtubatuba, South Africa, [4]Integrated Community-Based Initiatives, Kabwohe, Uganda, [5]Human Sciences Research Council, Sweetwaters, South Africa, [6]Duke Human Vaccine Institute, Durham, NC, USA*

**Background:** HIV viral load (VL) is a robust measure of antiretroviral therapy (ART) effectiveness and adherence and is used for clinical management of HIV. Dried blood spot (DBS) specimens of finger-prick blood transported at ambient temperature to a laboratory for VL testing can simplify ART monitoring while providing similar performance to plasma specimens (sensitivity: 91%, specificity: 99%, at 1000 copies/mL). However, DBS samples are typically obtained by providers, which limits ART monitoring outside the clinic.
**Methods:** In a randomized trial of community-based delivery of ART in KwaZulu-Natal, South Africa, (the DO ART Study) participants receiving community-based ART refills and monitoring provided plasma and two DBS specimens at their month-6 or -12 visit. Staff collected the first DBS specimen while training participants, and at the same visit, participants independently used a lancet and self-collected a second DBS specimen. These concurrently

collected specimens were transported 100-250 km to Global Labs (Durban) where VL was measured using the bioMérieux NucliSENS EasyQ HIV-1 assay. We compared 315 pairs of log-transformed DBS results from 261 participants using intraclass correlation coefficients (ICC) and scatterplots in R.
**Results:** The paired DBS results were highly correlated with an ICC of 0.98 (95% CI: 0.97-0.98). Twelve pairs of cards (4%) were discrepant at the limit of quantification (100 copies/mL): nine detected virus only on the staff-collected card and three only on the participant-collected card. Using the WHO threshold for viral suppression of 1000 copies/mL there were just two discrepant pairs (0.6%), one in either direction. There was high correlation between the plasma VL and results from both the staff-collected DBS (ICC: 0.94, 95% CI: 0.92-0.95) and participant-collected DBS (ICC: 0.92, 95% CI: 0.90-0.94). There were no clinically meaningful differences by gender or CD4 count.
**Conclusion:** Participant-collected DBS cards are highly comparable to those collected by clinical staff and could be used in a flexible, decentralized approach to population-based VL monitoring for ART adherence and response. The next step is to evaluate patient self-collection of DBS cards without staff supervision.

**Figure: Scatterplot of HIV viral loads from staff-collected vs participant-collected dried blood spot specimens**




* Values below the lower limit of quantification (100 copies/mL) are represented as 1 with random variation (jitter) applied to better visualize overlapping points.

## 813 INCREASED KNOWLEDGE OF HIV STATUS AMONG YOUTH:RESULTS OF YATHU YATHU RANDOMIZED TRIAL

Late Breaking

**Bernadette Hensen**[1], Sian Floyd[1], Mwelwa Phiri[2], Albertus Schaap[3], Lucheka Sigande[2], Melvin Simuyaba[2], Lawrence Mwenge[2], Rosemary Zulu-Phiri[2], Louis Mwape[2], Sarah Fidler[4], Richard Hayes[1], Musonda Simwinga[2], Helen Ayles[3]
*[1]London School of Hygiene & Tropical Medicine, London, UK, [2]Zambart, Lusaka, Zambia, [3]London School of Hygiene & Tropical Medicine, Lusaka, Zambia, [4]Imperial College London, London, UK*

**Background:** High quality evidence is urgently needed to inform the design of effective interventions to reduce the burden of HIV among adolescents and young people aged 15-24 (AYP), amongst whom HIV incidence remains high. Findings from HPTN-071 (PopART) in Zambia, community consultations and formative research with AYP, facilitated the co-development of Yathu Yathu, a strategy to deliver comprehensive sexual and reproductive health services (SRHS) to AYP in Lusaka, Zambia. We report the impact of Yathu Yathu on knowledge of HIV status.
**Methods:** Yathu Yathu was a cluster-randomized trial (CRT) conducted from 2019-2021 in two urban communities. The communities were divided into 20 zones (~2350 AYP/zone) that were randomly allocated to the Yathu Yathu intervention or control arm. In intervention zones, a community-based hub, staffed by peers, was established to provide SRHS. In 2019, a census was conducted in both arms; all consenting AYP aged 15-24 in both trial arms were given a Yathu Yathu card, which allowed AYP to accrue points for accessing SRHS at the hub and health facility (intervention), or the health facility only (control). Points could be exchanged for rewards, thus acting as an incentive to use SRHS in both arms. We conducted a cross-sectional survey in 2021 to estimate the impact of Yathu Yathu on the primary outcome: knowledge of HIV status (self-reporting living with HIV or HIV testing in the last 12 months). We analysed data at cluster-level using a two-stage process recommended for CRT with <15 clusters/arm.
**Results:** 1989 AYP consented to participate in the survey (50% male); consent was similar across arms (64% consent/arm). Across zones, knowledge of HIV status ranged from 63.6%-81.2% in intervention zones and from 35.4%-63.0% in control zones. Adjusting for age, sex and community, knowledge of HIV status was higher in the intervention arm compared to control (73.3% vs 48.4%, respectively, adjusted prevalence ratio (PR) 1.53 95%CI 1.36, 1.72; p<0.001). By age and sex, results were similar. However, the impact was greater among adolescents aged 15-19, particularly boys (62.2% vs 27.9%, PR=2.37 95%CI 1.77, 3.17; p<0.001).
**Conclusion:** Delivering incentivised, community-based peer-led SRHS increased knowledge of HIV status among all AYP compared with standard of care. Scaling up the Yathu Yathu strategy, shown to be a highly effective approach, has the potential to make a substantial contribution to increasing access to HIV prevention and care services for youth currently left behind.

| | Yathu Yathu Arm | Control Arm | Prevalence Ratio (95%CI) | Adjusted PR (95%CI) | p-value |
|---|---|---|---|---|---|
| Overall | 73.3% | 48.4% | 1.53 | 1.36, 1.72 | <0.001 |
| Adolescent girls (aged 15-19*) | 76.6% | 49.1% | 1.58 | 1.37, 1.83 | <0.001 |
| Adolescent boys (aged 15-19*) | 62.2% | 27.9% | 2.37 | 1.77, 3.17 | <0.001 |
| Women (aged 20-24*) | 84.4% | 65.7% | 1.33 | 1.05, 1.69 | 0.021 |
| Men (aged 20-24*) | 70.3% | 51.0% | 1.41 | 1.15, 1.73 | 0.002 |

*Age at time of consent to receive a Yathu Yathu card

## 814 3-IN-1 RAPID BLOOD SELF-TESTING FOR HIV, HBV, AND HCV: ACCEPTABILITY AND FEASIBILITY

**Nicolas Salvadori**[1], Jullapong Achalapong[2], Chonlatorn Boontan[3], Surachet Arunothong[3], Woottichai Khamduang[1], Phornphimon Moolnoi[1], Sakorn Pornprasert[1], Sumet Ongwandee[3], Jean Yves Mary[4], Gonzague Jourdain[5], Nicole Ngo-Giang-Huong[5]
*[1]Chiang Mai University, Chiang Mai, Thailand, [2]Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand, [3]Office of Disease Prevention and Control Region 1 Chiang Mai, Department of Disease Control, Ministry of Public Health, Chiang Mai, Thailand, [4]INSERM U1153, Team ECSTRA, Université Paris Diderot - Paris 7, Hôpital Saint-Louis, Paris, France, [5]MIVEGEC, Université Montpellier, CNRS, IRD, Montpellier, France*

**Background:** Early diagnosis is key to achieving the triple goal of eliminating transmission of HIV, hepatitis B and C. We assessed the acceptability, feasibility and interpretability of facility-based self-testing using a 3-in-1 rapid diagnostic test (RDT).
**Methods:** Client-initiated testing services were provided free of charge to consenting individuals aged at least 15 years in one of four facilities in northern Thailand as part of a research project (NCT04585165). To decrease costs, optimize time spent and limit physical contacts in pandemic times, clients were invited to choose between self-testing by fingerprick or blood collection by a healthcare worker (HCW) using TriQuik™ (Genlantis, CA, USA), a single-strip RDT for HIV-1/2 antibody, hepatitis B surface antigen and hepatitis C antibody. Several clients could simultaneously self-test in separate, private areas. After completing a sociodemographic and behavioral questionnaire on a tablet computer, clients followed self-test video instructions, took a picture of the test results for electronic review by the HCW, and reported their interpretation of the results and their satisfaction level. When the HCW interpreted a HIV self-test as positive, the HCW collected blood by venipuncture for confirmation with two other antibody tests. All self-test results interpreted as positive by the client and as negative by the HCW were retrospectively reviewed by a second HCW.
**Results:** Between October 19, 2020 and September 28, 2021, of 2,260 clients presenting for testing for the first time as part of the project, 1,844 (82%) chose self-testing. 909 (49%) self-testers were born male, of whom 321 have sex with men (311 cisgender men and 10 transgender women). Median age was 27 years (IQR, 22-34). 1,751 (>99% of those who answered) were satisfied with the self-testing process. Of 5,532 self-test results, 70 (1%) disagreements were observed among 37 (2%) clients (see Table). All self-tests interpreted as positive by the client and as negative by the HCW were retrospectively interpreted as negative by a second HCW. All HIV self-tests interpreted as positive by the HCW were confirmed positive by two other antibody tests.
**Conclusion:** The choice between self- and conventional testing using a 3-in-1 RDT was very well perceived. Multiplex self-testing decreased costs but may have increased opportunities for client misinterpretations. Having a HCW

available to supervise several clients may be a cost-efficient strategy to ensure reliable results and public trust.

| Test result interpretation | | | By healthcare worker | |
|---|---|---|---|---|
| | | | Positive | Negative |
| HIV-1/2 antibody | By client | Positive | 34 | 26 |
| | | Negative | 1 | 1,779 |
| | | Invalid | 0 | 1 |
| | | Client did not interpret | 0 | 3 |
| Hepatitis B surface antigen | By client | Positive | 54 | 15 |
| | | Negative | 3 | 1,768 |
| | | Invalid | 0 | 1 |
| | | Client did not interpret | 1 | 2 |
| Hepatitis C antibody | By client | Positive | 3 | 13 |
| | | Negative | 0 | 1,824 |
| | | Invalid | 0 | 1 |
| | | Client did not interpret | 0 | 3 |

## 815 INCREASE IN FALSE POSITIVE 4TH GENERATION HIV TESTS IN PATIENTS WITH COVID-19 DISEASE

**Anita Shallal**[1], Smitha Gudipati[1], Edward Peterson[1], Bernard Cook[1], Robert Tibbetts[1], Norman Markowitz[1]
*[1]Henry Ford Hospital, Detroit, MI, USA*

**Background:** A variety of infections and inflammatory conditions have been associated with false positive (FP) serological tests, including those for HIV. In the context of an HIV counseling, testing, and referral program, an apparent increase in FP 4th generation HIV tests was observed among persons infected with SARS-CoV-2. We sought to determine if there was an association of active coronavirus disease-2019 (COVID-19) with a FP HIV test.
**Methods:** This was a retrospective, cross-sectional study from March 2020 to August 2021 at Henry Ford Hospital. Through electronic medical record extraction, all results for SARS-CoV-2 by PCR within + two weeks of a diagnostic HIV 4th generation assay (Elecsys HIV Duo, Roche Diagnostics, Indianapolis, IN) were selected. Confirmatory HIV-1 and HIV-2 antibodies, as well as quantitative HIV RNA, was performed for all positive 4th generation tests. All positive HIV 4th generation assays were independently reviewed and divided into groups of FP, true positives (TP), and true negatives (TN). Variables included age, race, ethnicity, and sex. Statistical analysis was performed in a pairwise fashion using a Chi-squared test. Multivariate logistic regression was used to predict positive COVID-19 tests.
**Results:** A total of 23,278 medical records meeting the above criteria were reviewed. The rates of COVID positive tests were then arranged in groups of HIV TP, FP, and TN. In total, 23,041 patients had a TN HIV test result, 167 patients had a TP, and 70 patients had a FP (Table 1). Those with HIV FP tests had the highest percentage of COVID positive test results at 22.9% (p=0.001), which was significantly higher than HIV TN (10.2%; p=0.197) and HIV TP (7.2%; p=0.001). After adjustment for all covariates, only FP HIV was significantly associated with COVID-19 (OR=7.04; p=0.001).
**Conclusion:** This study reveals that patients with active COVID-19 disease are significantly more likely to have a false positive 4th generation HIV test. The mechanism for this is unknown but may reflect broad polyclonal antibody generation in acute infections or cross-reactivity to antibodies with the SARS-CoV-2 spike protein. Although only a single 4th generation test was evaluated in this study, acute COVID-19 infection should be considered as a potential etiology for a false positive 4th generation HIV test.

**Table 1. Chi-squared test of COVID positive tests in groups of HIV 4th generation true positives, false positives, and true negatives**

| | | HIV 4th Generation Test N (%) | | | Overall p-value |
|---|---|---|---|---|---|
| | | True Positive | False Positive | True Negative* | |
| SARS-CoV-2 PCR Test | Positive | 12 (7.2) | 16 (22.9) | 2,354 (10.2) | 0.005 |
| | Negative | 155 (92.8) | 54 (77.1) | 20,687 (89.7) | |
| | Total | 167 | 70 | 23,041 | |

[HIV: human immunodeficiency virus; SARS-CoV-2: severe acute respiratory distress coronavirus-2; PCR: polymerase chain reaction]
*Estimated true negative

## 816 NEW MOLECULAR ASSAY BASED ON NANOTECHNOLOGY FOR THE EARLY DETECTION OF HIV-1 p24

New Investigator Scholar

**Ana Rodríguez Galet**[1], Sergio García López[2], Priscila Kosaka[2], África Holguín[1]
*[1]Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain, [2]Instituto de Microelectrónica de Madrid, Madrid, Spain*

**Background:** Early HIV detection (first 6 months) is key to control HIV pandemic. Primary infection comprises both acute and early infection, and acute infection 5 phases (eclipse/Fiebig stages I-IV) until seroconversion. HIV-1 P24 capsid protein can be detected by 4th-5th generation screening immunoassays, detecting ≈10pg/mL P24 (≈105 virions), allowing diagnosis 3–4 weeks after infection. We present the first evaluation of a biosensor based on gold-plasmonic nanoparticles for P24 detection in samples from early and chronic infection with different HIV variants.
**Methods:** A new plasmonic immunoassay was used to detect 23 plasmas from patients in different HIV-1 early infection stages (4 Eclipse/19 Fiebig I-V; Panel-0800-0297-Seracare), in 25 culture supernatant with different HIV-1 subtypes and recombinants (Eqapol Genetic Diversity panel), and in 6 paired plasma/DBS from subjects in chronic infection (viremia <1.6-4.15log cop/ml). The measurement by duplicate of the plasmonic response used AVAC scanner platform (Mecwins). The gold nanoparticles were optically identified, and their scattering was analyzed to characterize, classify and count the nanoparticles present on the silicon surface due P24 detection with high specificity. Capture anti-P24-IBAB1 antibodies were used on the silicon surface and detection-anti-P24-IBAB12-antibodies (Infinity-Biomarkers) conjugated to carboxyl-polymer coated 100nm-diameter gold nanoparticles (Nanopartz).
**Results:** The new biosensor showed extreme sensitivity for P24 detection at early stages, undetectable by nucleic acid technologies (NAATs), detecting 50% of Eclipse Stage, all Stage I, and all but one samples in chronic infection. The rates of false-negative samples increased in Stage II-V samples. The LOD of the new P24 assay was 10ag/mL (10—5pg/mL), equivalent to one virion in 100µl of plasma (10 virions/ml). This sensitivity is 5 orders of magnitude better than the first approved 5th immunoassay (7.02pgP24/ml, BioPlex-BioRad) and 2 orders of magnitude better than NAATs. The assay also detected P24 in all DBS/Plasma pairs, and in 11 (44%) Eqapol samples, being the remaining not detected, undetermined or discarded by biosensor surface contamination by analytes in supernatants.
**Conclusion:** We present a new molecular nanotechnology able to detect HIV in plasma and DBS specimens from acute infection, even in the first week, before any commercial serological or molecular assay. Further research is required to adapt this new tecnology at low cost and the point-of-care.

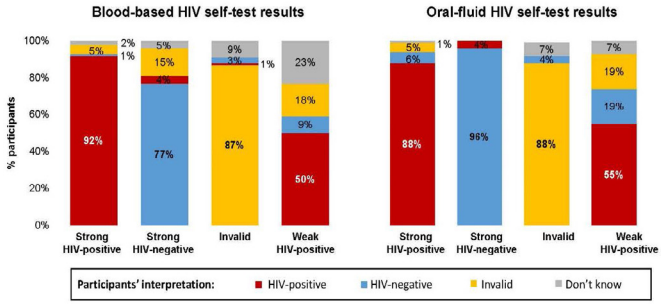
## 817 INTERPRETATION OF HIV SELF-TEST RESULTS AMONG PrEP USERS IN KENYA

**Peter A. Mogere**[1], Ashley Bardon[2], Dorothy Mangale[2], Catherine Kiptinness[1], Richard Magara[1], Snaidah Ongachi[1], Sarah Mbaire[1], Stephen Gakuo[1], Nelly R. Mugo[1], Jared Baeten[3], Katrina Ortblad[4], Kenneth Ngure[5]
*[1]Kenya Medical Research Institute, Nairobi, Kenya, [2]University of Washington, Seattle, WA, USA, [3]Gilead Sciences, Inc, Foster City, CA, USA, [4]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [5]Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya*

**Background:** Clients on PrEP are recommended to test for HIV every three months to detect any potential breakthrough infections. HIV self-testing (HIVST) has the potential to support PrEP continuation by moving regular HIV testing from the clinic to the home. We measured how well PrEP clients in Kenya could interpret HIVST results to understand the feasibility for this differentiated model of PrEP delivery.
**Methods:** We used data from the intervention arms of the JiPime-JiPrEP study, a 3-arm randomized trial testing a model of 6-month PrEP dispensing supported with interim HIVST at 3 months (NCT03593629). Eligible participants were ≥18 years and been using PrEP for 1 month. Participants in the intervention arms received a 6-month PrEP supply and either two blood-based (BB) or oral-fluid (OF) HIV self-tests. Additionally, at enrollment they received HIVST training and completed a BB or OF self-test (depending on their assignment) with the guidance of a clinical provider. At 6 months, participants were asked to interpret pre-printed mock colored images of BB or OF HIVST results (strong HIV-positive; strong HIV-negative; invalid; weak HIV-positive) presented in a random order; participants only interpreted images of the self-test assigned to them. We used descriptive statistics to report how well participants interpreted HIVST results.
**Results:** From November 2018 to December 2020, 83% (137/166) of participants in the BB HIVST arm, and 84% (137/163) of participants in the OF HIVST returned for follow-up and interpreted images of HIVST results at 6 months. These participants had a median age of 33 years (IQR 28-41) and 8 years in school (IQR 8-12). Among participants in the BB HIVST arm, correct interpretation of strong-positive results was 92% (126/137), and strong-negative results was 77% (105/137). Among participants in the OF HIVST arm, correct interpretation of strong HIV-positive results was 88% (121/137) and strong HIV-negative results was 96% (132/137). In both arms, participants' correct interpretation of invalid and weak HIV-positive results was similar (invalid: 87-89%; weak HIV-positive: 50-55%), Figure 1.

**Conclusion:** While most PrEP users correctly interpreted HIVST results, incorrect interpretation was not uncommon despite personalized HIVST training and prior use experience. More research is needed to understand ways to support clients' interpretation of HIVST results to ensure the quality of future community-delivered HIV services supported with HIVST.

**Fig. 1** – HIVST result interpretation by participants per arm.




## 818 LIMIT OF DETECTION OF SARS-CoV-2 ANTIBODY ASSAYS

New Investigator Scholar

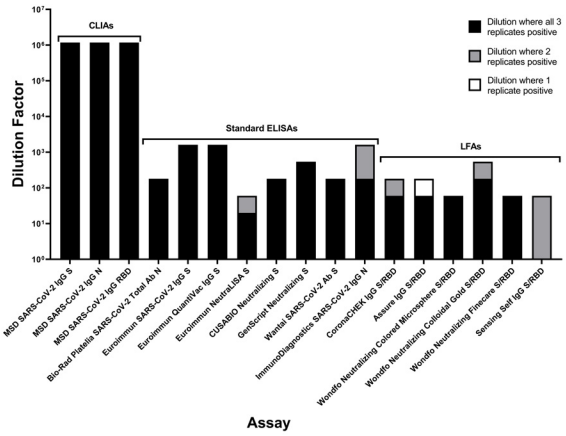
**Evan Beck**[1], Santosh Dhakal[2], Sharada Saraf[1], Reinaldo Fernandez[2], Owen R. Baker[2], Sabra L. Klein[2], Thomas Quinn[1], Oliver Laeyendecker[1]
[1]*National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA,* [2]*The Johns Hopkins University, Baltimore, MD, USA*

**Background:** Seroprevalence studies of antibodies to SARS-CoV-2 are important for public health surveillance. Recent studies have shown that antibodies to SARS-CoV-2, both from natural infection and vaccination, decrease with time from exposure. Variation in the performance of antibody assays will impact the estimates of SARS-CoV-2 exposure and vaccination levels in a population. Using standardized serial dilutions, we evaluated 17 SARS-CoV-2 assays to establish an approximate limit of detection for each assay.

**Methods:** The evaluated assays consisted of three chemiluminescent immunoassays (CLIAs), eight standard enzyme-linked immunosorbent assays (ELISAs), and six lateral flow assays (LFAs). All assays either evaluated IgG antibodies or total antibodies to SARS-CoV-2. The target antigen of 14 assays was the spike protein (S) or receptor binding domain (RBD); three assays evaluated antibodies to the nucleocapsid protein (N). A human SARS-CoV-2 serology standard with a WHO SARS-CoV-2 Serology International Standard binding antibody units (BAU) value of 764 BAU/mL to spike IgG and 681 BAU/mL to nucleocapsid IgG was obtained from the Frederick National Laboratory for Cancer Research. Half-logarithmic serial dilutions of the standard were then run in triplicate on each assay.

**Results:** The MSD V-Plex chemiluminescent immunoassays (CLIAs) were the most sensitive by three logs, with positive results at a dilution greater than 1:106 (Figure). Standard ELISAs were less sensitive, with limits of detection ranging from dilutions of 1:20 (Euroimmun NeutraLISA) to 1:1620 (Euroimmun SARS-CoV-2 IgG and Euroimmun QuantiVac). Lateral flow assays (LFAs) were the least sensitive, with only one assay (Wondfo Colloidal Gold) having at least one positive result with a dilution greater than 1:180.

**Conclusion:** As population seroprevalence to SARS-CoV-2 continues to rise, tests with a high limit of detection will be crucial for surveillance studies. As antibody levels decline after vaccination or infection, our data indicate that CLIAs like the MSD assay may provide the best opportunity to capture asymptomatic cases and individuals with low antibody titers.




## 819 MSD V-PLEX SARS-CoV-2 ASSAY TO IDENTIFY VACCINATED AND INFECTED INDIVIDUALS

New Investigator Scholar

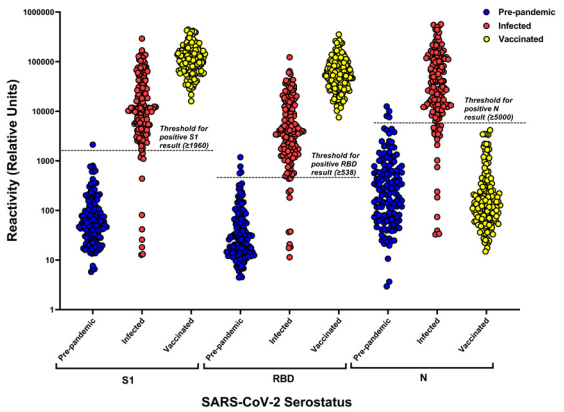
**Evan Beck**[1], Andrew Karaba[2], Xianming Zhu[2], Ruchee Shrestha[2], Aaron M. Milstone[2], Andrew Redd[1], Aaron Tobian[2], Evan M. Bloch[2], Emily Egbert[2], Joel Blankson[2], Yu-Hsiang Hsieh[2], Richard Rothman[2], Thomas Quinn[1], Oliver Laeyendecker[1]
[1]*National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA,* [2]*The Johns Hopkins University, Baltimore, MD, USA*

**Background:** The prevalence of vaccinated, previously infected, and individuals at risk of SARS-CoV-2 infection is important for epidemiologic studies and public health interventions. Asymptomatic infections and reluctance to disclose vaccination status hinder accurate assessments of the current state of the epidemic. Since COVID-19 vaccines generate immune responses to spike (S1), but not nucleocapsid (N), it is possible to differentiate between vaccinated, infected, and unexposed individuals by comparing antibody reactivity to each antigen. The MSD V-Plex SARS-CoV-2 IgG assay can potentially differentiate each state in one test by simultaneously evaluating IgG reactivity to the S1, receptor binding domain (RBD), and N proteins.

**Methods:** The MSD assay was validated with three sample sets: known vaccination with no previous infection (n=158); known infected and not vaccinated (n=157); and samples collected prior to the COVID-19 pandemic in 2016 (n=144). Of the previously infected individuals, 15 (9.6%) were hospitalized; sample collection occurred a median of 48 days after a PCR-positive result. Using an algorithm, samples with positive results on both S1 and RBD but negative on N were classified as vaccinated. Samples with a positive result on all three proteins were considered to be infected with the possibility of subsequent vaccination. Any other result was classified as unexposed. Sensitivity and specificity for each state were calculated.

**Results:** Reactivity to each antigen is shown in the figure. 100% (95% confidence interval [CI] 97.7-100), 92% (95% CI 86.3-95.5), and 0.7% (95% CI 0.02-3.8) of vaccinated, infected, and unexposed samples were positive for S1. 100% (95% CI 97.7-100.0%), 91% (95% CI 85.5-95.0%), and 0.7% (95% CI 0.02-3.8%) of vaccinated, infected and unexposed samples were positive for RBD. 0% (95% CI 0-2.3), 86% (95% CI 79.6-91.0), and 2.1% (95% CI 0.4-6.0) of vaccinated, infected and unexposed samples were positive for N. Algorithm sensitivity and specificity for classification of vaccinated samples were 100% (95% CI 97.7-100) and 96.7 (95% CI 94-98.4). For the classification of samples from previously infected individuals, sensitivity and specificity were 83.4% (95% CI 76.7-88.9) and 100% (95% CI 98.8-100).

**Conclusion:** This study establishes the sensitivity and specificity for a high-throughput assay ideal for SARS-CoV-2 seroprevalence studies. Future research should focus on applying this assay in health care settings to guide practice and policy to mitigate the pandemic.




## 820 COMPARISON OF SARS-CoV-2 LIVE VIRUS NEUTRALIZATION AND SEROLOGIC IMMUNOASSAYS

New Investigator Scholar

**Owen R. Baker**[1], Eshan U. Patel[2], Andrew Pekosz[2], Kirsten Littlefield[2], Reinaldo Fernandez[1], Aaron Tobian[1], Evan M. Bloch[1], Yu-Hsiang Hsieh[1], Richard Rothman[1], Andrew Redd[3], Thomas Quinn[3], Oliver Laeyendecker[3]

*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

**Background:** Live virus micro-neutralization (MN) is the gold standard for quantifying the neutralizing titer (NT) of antibodies to SARS-CoV-2. However, performing MN is labor intensive and requires a biosafety level 3 laboratory. We assessed the performance of 8 immunoassays which measure SARS-CoV-2 NT and compared them to gold standard MN results.

**Methods:** Samples from 269 individuals known to previously be SARS-CoV-2 PCR+ (i.e., convalescent individuals, <10% hospitalized) and 200 pre-pandemic individuals were evaluated on 3 lateral flow immunoassays (LFAs; Wondfo Colloidal Gold, Wondfo Colored Microsphere, Wondfo Finecare) and 5 enzyme-linked immunoassays (ELISAs; ImmunoRank, GenScript, Cusabio, Euroimmun NeutraLISA, Euroimmun QuantiVac). MN was performed on all samples from convalescent individuals; results were classified as undetectable vs any detection of MN NT (NT<20 vs. NT>20), as well as high and low MN NT (NT>80 vs. NT<80). Receiver operating curve analysis was used to assess accuracy for detecting levels of NT. The area under the curve (AUC) was calculated for the manufacturer's cut off and empirically to identify the best discriminatory cut off value. Cohen's kappa statistics were calculated to assess categorical agreement and Spearman's rank statistics were calculated to assess correlations.

**Results:** Of the 269 convalescent plasma samples, 89 (33%) had MN NT values <20 (undetectable) and 117 (43%) >80 (high NT). Using the manufacturer's cutoffs, sensitivity for detection of samples with any NT ranged from 79% to 100%, and the false-positive rate (ie, classifying samples with undetectable NT as positive) was highest for LFAs (72% to 84%) and ranged from 14% to 69% for the ELISAs. For all assays except the ImmunoRank and NeutraLISA ELISAs, discrimination to identify samples with any NT was improved by raising the cut off values (Table). AUCs of ~0.94 to discriminate high NT samples could be achieved for all quantifiable assays using an adjusted cut off value. Cohen's kappa statistic ranged from 0.20 to 0.69. Spearman's rank correlation between each assay and NT value ranged from 0.73 to 0.86. Using the manufacturer's cutoffs, specificity on pre-pandemic samples was ≥98% for all assays except for Cusabio which was 86%.

**Conclusion:** The performance of immunoassays using manufacturer's cutoff to discriminate samples with any NT was accurate (AUC>0.83 for all assays), but could be improved by changing the cutoff. Identifying samples with high NT could be achieved using an alternative cutoff.

Table. Comparison and correlation of serologic assays claiming to measure neutralizing antibody titer to SARS-CoV-2 with live virus micro-neutralization assay in convalescent SARS-CoV-2 PCR+ individuals (n=269).

| | Manufacturer's Cutoff | Empirical Analysis | | | |
|---|---|---|---|---|---|
| | Any NT | Any NT | High NT | Agreement Analysis | |
| Serologic Assay | Cut off; AUC (95% CI) | Cut off; AUC (95% CI) | Cut off; AUC (95% CI) | Spearman's Rank | Cohen's Kappa |
| Wondfo Colloidal Gold | visual; 0.88 (0.85, 0.90) | - | - | - | 0.33 |
| Wondfo Colored Microsphere | visual; 0.87 (0.85, 0.90) | - | - | - | 0.24 |
| Wondfo Finecare | 1.0; 0.87 (0.84, 0.89) | 8.6; 0.97 (0.96, 0.98) | 29.9; 0.94 (0.92, 0.96) | 0.74 | 0.20 |
| ImmunoRank | 20.0; 0.87 (0.84, 0.90) | 16.2; 0.97 (0.95, 0.98) | 25.1; 0.94 (0.92, 0.96) | 0.77 | 0.60 |
| Cusabio | 20.0; 0.83 (0.80, 0.86) | 46.7; 0.96 (0.94, 0.97) | 64.1; 0.92 (0.89, 0.94) | 0.73 | 0.34 |
| GenScript | 20.0; 0.89 (0.86, 0.91) | 43.3; 0.98 (0.97, 0.99) | 61.7; 0.95 (0.93, 0.97) | 0.82 | 0.36 |
| NeutraLISA | 35.0; 0.90 (0.87, 0.93) | 11.3; 0.97 (0.96, 0.99) | 24.3; 0.94 (0.92, 0.97) | 0.82 | 0.68 |
| QuantiVac | 35.2; 0.88 (0.86, 0.91) | 64.7; 0.97(0.96, 0.99) | 127; 0.95 (0.93, 0.97) | 0.81 | 0.45 |

## 821 DEVELOPMENT OF A HIGH-THROUGHPUT NGS WORKFLOW FOR SARS-CoV-2 WHOLE-GENOME SEQUENCING

**Sun Hee Rosenthal**[1], Anna Gerasimova[1], Rolando Ruiz-Vega[1], Kayla Livingston[1], Ron M. Kagan[1], Yan Liu[1], Ben P. Anderson[1], Renius Owen[1], Laurence E. Bernstein[1], Alla Smolgovsky[1], Dong Xu[1], Rebecca Chen[1], Andrew Grupe[1], Pranoot Tanpaiboon[1], Felicitas L. Lacbawan[1]

*[1]Quest Diagnostics, San Juan Capistrano, CA, USA*

**Background:** Monitoring new mutations in SARS-CoV-2 is crucial for identifying diagnostic and therapeutic targets and important insights to achieve a more effective COVID-19 control strategy. Next-generation sequencing (NGS) has been widely used for whole-genome sequencing of SARS-CoV-2. However, NGS methods may be limited by the complexity of workflow, which limits scalability. Here, we address this limitation by designing a workflow optimized for high-throughput studies.

**Methods:** We utilized modified ARTIC network v3 primers for SARS-CoV-2 whole-genome amplification. Similar to a previously reported tailed PCR approach, libraries were prepared by a 2-step PCR method but optimized to improve amplicon balance, integrate robotic liquid handlers, and minimize amplicon dropout for viral genomes harboring primer-binding site mutation(s). Sequencing was performed on the Illumina NovaSeq 6000 and the Illumina MiSeq. An in-house analysis pipeline utilized the BWA aligner and iVar software. Assay precision was assessed with unique clinical samples. Assay sensitivity was assessed with serial dilutions of clinical samples. Robustness was assessed by sequencing samples and controls on the NovaSeq from multiple prior ARTIC v3 runs.

**Results:** Intra-assay (n=188) and inter-assay (n=168) precision at the amino acid substitution level was 99.8% and 99.5%, respectively. Over 98.2% (111/113) of samples with a cycle threshold (Ct) <28 yielded a near-complete (≥97%) consensus sequence, and 98.7% (147/149) of samples with a Ct <30 yielded ≥90% consensus coverage. 2,688 samples and controls were sequenced in a single NovaSeq run yielding a 94.3% (2,416/2,562) sample pass rate. The optimized workflow gave more complete SARS-CoV-2 genome consensus sequences for most viral clades than the original ARTIC v3 workflow (Table). From over 65,000 clinical samples sequenced in 2021, we observed clade and lineage prevalence in-line with those documented by the CDC in 2021, including the Alpha clade that peaked at 65.3% in May, and the Delta clade that attained near-100% prevalence in September.

**Conclusion:** We present an optimized workflow to process up to 2,688 samples in a single NovaSeq 6000 run without compromising sensitivity or robustness and with fewer amplicon dropout events compared to the standard ARTIC protocol. We additionally report results for over 65,000 SARS-CoV-2 clinical specimens collected in the United States between January and September of 2021, as part of an ongoing national genomics surveillance effort.

**Proportion of SARS-CoV-2 samples generating complete consensus sequence with the automated high-throughput SARS-CoV-2 workflow, by clade**

| | Samples generating complete consensus sequence with each workflow, Complete/Total (%)[1] | |
|---|---|---|
| Clade[2] | High-throughput workflow[3] | ARTIC v3 workflow[4] |
| 19B | 100 (3/3) | 0 (0/3) |
| 20A | 83.0 (44/53) | 62.2 (33/53) |
| 20B | 96.2 (102/106) | 59.4 (63/106) |
| 20C | 88.7 (87/98) | 47.9 (47/98) |
| 20G | 96 (168/175) | 81.1 (142/175) |
| 20H (Beta, V2) | 100 (7/7) | 0 (0/7) |
| 20I (Alpha, V1) | 96.9 (691/713) | 78.2 (558/713) |
| 20J (Gamma, V3) | 100 (44/44) | 45.4 (20/44) |
| 21A (Delta) | 100 (1/1) | 0 (0/1) |
| 21C (Epsilon) | 98.0 (99/101) | 0.99 (1/101) |
| 21D (Eta) | 100 (10/10) | 100 (10/10) |
| 21F (Iota) | 97.7 (128/131) | 61.8 (81/131) |
| 21G (Lambda) | 100 (1/1) | 0 (0/1) |
| 21H | 100 (3/3) | 66.6 (2/3) |
| Total | 95.9 (1,387/1,446) | 66.1 (957/1,446) |

[1] Complete consensus sequence as defined by obtaining ≥97% SARS-CoV-2 genome coverage.

[2] SARS-CoV-2 clades were assigned with Nextclade (https://clades.nextstrain.org/).

[3] Samples were sequenced on the Illumina NovaSeq 6000 with the SP reagent kit using 2 x 251 cycles.

[4] Samples were sequenced on the Illumina MiSeq with the 600 cycle v3 kit using 2 x 251 cycles.

## 822 ORAL SALIVA SWAB RT-PCR AS A FIT-FOR-PURPOSE DIAGNOSTIC TEST FOR COVID-19 IN CHILDREN

**Cinta Moraleda**[1], Sara Domínguez-Rodríguez[1], Juan Miguel Mesa[2], Paula García[3], Jose Antonio Alonso[4], Amanda Bermejo[5], Gema Sabrido[6], Leticia Martínez-Campos[7], María De la Serna[8], Arantxa Gonzalez[9], Álvaro Ballesteros[1], Juan Carlos Galán[10], Francisco Llorente[11], Alfredo Tagarro[1]

[1]Fundación para la Investigación Biomédica del Hospital 12 de Octubre, Madrid, Spain, [2]Paediatrics Department. Hospital Universitario Infanta Sofía, Madrid, Spain, [3]Hospital Universitario La Paz, Madrid, Spain, [4]Emergency Pediatrics Department, Hospital Infantil Universitario Niño Jesús, Madrid, Spain, [5]Hospital Universitario de Móstoles, Móstoles, Spain, [6]Hospital Universitario Rey Juan Carlos, Móstoles, Spain, [7]Hospital Universitario Torrecárdenas, Almería, Spain, [8]IBM Research–Zurich, Zurich, Switzerland, [9]Hospital Universitario 12 de Octubre, Madrid, Spain, [10]Microbiology Departament, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain, [11]Center de Investigation en Sanidad Animal (Animal Health Research Center) INIA-CSIC, Madrid, Spain

**Background:** Testing using nasopharyngeal swabs (NPS) samples is the cornerstone for the control of the COVID-19 pandemic, but the procedure is uncomfortable and generates anxiety, especially in children. We aimed to evaluate the adequacy of oral saliva swab analysis using RT-PCR comparing to NPS by RT-PCR and Antigen Rapid Test (AgRT) on NPS in children.

**Methods:** Cross-sectional multicenter diagnostic study nested in a prospective, observational cohort (EPICO-AEP) carried out between February and March 2021 at 10 hospitals in Spain. Participants were children 0 to 18 years old with symptoms compatible with SARS-CoV-2 infection of ≤5 days of duration attending at emergency departments. Three samples were collected, two NPS (for AgRT and for RT-PCR) and one oral saliva swab for RT-PCR. In patients with discordant results, new NPS was collected for viral culture and original samples were tested for viral RNA subgenomic (sgRNA) study.

**Results:** 1174 children were included in the analysis, aged 3.8 years (IQR, 1.7-9.0), 647/1174 (55.1%) were male and 760/1174 (64.7%) presented fever 1 day before emergency department admission (IQR 1.0-2.0). Overall, 73/1174 (6.2%) patients tested positive in at least one of the techniques. Sensitivity for RT-PCR in oral saliva swab was 72.1% (95%CI, 59.7-81.9) and specificity 99.6% (95%CI, 99.0-99.9); AgRT in NPS was 61.8% (95%CI, 49.1-73.0) and 99.9% (95%CI, 99.4-100). Kappa index for RT-PCR oral saliva swab was 0.80 (95%CI, 0.72-0.88), and for AgRT was 0.74 (95%CI, 0.65-0.84) vs RT-PCR in NPS. A Bayesian model was used to estimate the accuracy assuming that RT-PCR in NPS is not a perfect gold standard. In this model, sensitivity for RT-PCR oral saliva swab was 84.8% (95%Cr 71.5-93.6), and for AgRT, it was 72.5% (95%Cr, 58.8-83.6). Specificity for RT-PCR oral saliva swab was 99.7% (95%Cr, 99.2-99.9), and for AgRT it was 99.9% (95% Cr, 99.6-100). The Cts were higher in oral saliva swabs compared with NPS; being Ct (NPS)=0.5 x (Ct saliva) + 4.5 (p=0.027). Overall, 4 (10.8%) patients with discordant results had a positive culture. In 3 of the 4 patients, the discordance consisted of positive result on oral saliva swab and nasopharyngeal swabs RT-PCR but negative by antigen rapid diagnostic test. No patient had (+) culture, (+)NP, (-)oral swab.

**Conclusion:** RT-PCR on oral saliva swab is an accurate option for SARS-CoV-2 testing in children. A friendlier technique for younger patients, who must be tested very frequently, may help to increase the number of patients tested.

Diagnostic accuracy and agreement of oral saliva swab RT-PCR and rapid antigen test compared with nasopharyngeal swab RT-PCR using a Bayesian latent class model

| Parameters | RT-PCR NPS (assumed as a perfect gold standard (%) * | Bayesian latent class model (%) ** |
|---|---|---|
| Prevalence | 5.8 (4.6 - 7.3) | 5.0 (3.8 - 6.4) |
| RT-PCR NPS | | |
| Sensitivity | 100 | 99.3 (92.1 - 100) |
| Specificity | 100 | 99.1 (98.3 - 99.7) |
| Positive Predictive Value | 100 | 84.4 (73.3 - 94.6) |
| Negative Predictive Value | 100 | 100 (99.6 - 100) |
| RT-PCR oral saliva swab | | |
| Sensitivity | 72.1 (59.7 - 81.0) | 84.8 (71.5 - 93.6) |
| Specificity | 99.6 (99.0 - 99.9) | 99.7 (99.2 - 99.9) |
| Positive Predictive Value | 92.5 (80.9 - 97.6) | 92.6 (83.3 - 98.3) |
| Negative Predictive Value | 98.3 (97.3 - 98.9) | 99.2 (98.4 - 99.7) |
| Antigen Rapid Test | | |
| Sensitivity | 61.8 (49.1 - 73.0) | 72.5 (58.8 - 83.6) |
| Specificity | 99.9 (99.4 - 100) | 99.9 (99.6 - 100) |
| Positive Predictive Value | 97.7 (86.2 - 99.9) | 97.6 (89.9 - 100) |
| Negative Predictive Value | 97.7 (96.6 - 98.5) | 98.6 (97.6 - 99.2) |

* Gold standard model assumed that RT-PCR NPS test is perfect (100% sensitivity and 100% specificity; all patients with positive gold standard test are diseased and all patients with negative gold standard test are non-diseased). Values shown are estimated means with 95% confidence interval.

** Bayesian latent class model assumed that all tests evaluated are imperfect. Values shown are estimated median with 95% credible interval.

RT-PCR: reverse transcriptase polymerase chain reaction; NPS: nasopharyngeal swab;

## 823 UTILITY OF COVID-19 POINT-OF-CARE ANTIGEN TESTS IN LOW-MIDDLE INCOME SETTINGS

**Ameena Goga**[1], Elizabeth S. Mayne[2], Kubashni Woeber[1], Simbarashe Takuva[3], Duduzile Nsibande[1], Molebogeng Lekalakala[2], Shameem Jaumdally[4], Portia Mutevedzi[5], Helena Vreede[6], Brodie Daniels[7], Clement Kufe[2], Keertan Dheda[4], Kamy Chetty[2], Glenda E. Gray[1]

[1]South African Medical Research Council, Cape Town, South Africa, [2]National Health Laboratory Service, Johannesburg, South Africa, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [4]University of Cape Town, Cape Town, South Africa, [5]University of Witwatersrand, Johannesburg, South Africa, [6]National Health Laboratory Service, Cape Town, South Africa, [7]South African Medical Research Council, Durban, South Africa

**Background:** Access to SARS-CoV-2 polymerase chain reaction (PCR) testing is a bottleneck globally, especially in low- and middle-income countries (LMICs). Reliable point-of- care (POC) diagnostics for coronavirus disease 2019 (COVID-19) are cheaper and easier to scale-up than PCR especially in LMICs, and will facilitate interruption of transmission. We report the field-based effectiveness of rapid point-of-care (POC) antigen COVID-19 tests during the beta and delta waves, in South Africa.

**Methods:** We enrolled symptomatic, ambulatory persons under investigation (PUIs) aged 18 years and older, presenting for SARS-CoV-2 diagnosis at public health facilities in three provinces, South Africa. All patients completed a questionnaire regarding symptoms. Nasopharyngeal swabs were taken and processed for SARS-CoV-2 PCR testing using either GeneXpert (Cepheid, USA), or with a manual assay (ThermoFisher TaqPath assay or Seegene Allplex assay) on a real-time PCR platform at routine, accredited National Health Laboratory Service laboratories, as per routine national protocols. Concomitantly, trained study staff performed three facility-based POC antigen tests on a nasal/nasopharyngeal swab, as recommended by the manufacturer. Asymptomatic contacts of people with confirmed COVID-19 were recruited into the asymptomatic study arm and rapid tests and PCR were performed. The sensitivity (S), specificity (Sp), positive (PPV) and negative predictive (NPV) values of tests for PUIs and contacts were calculated using PCR as the reference standard.

**Results:** Between Oct 2020-2021 1816 participants were enrolled; 472 (26%) tested PCR or rapid test positive; 235 positives (49.8%) and 532 negatives were followed up at 5-14 days; 574 asymptomatic contacts were enrolled, of which 21 (3.7%) were PCR positive. Performance of the three antigen tests are shown in Table 1*.

**Conclusion:** In a real world setting, during the beta and delta waves, compared with PCR the sensitivity of rapid antigen tests ranged from 35-68%. This may reflect low viral loads at diagnosis. Further work will compare antigen test performance in patients with high versus lower cycle threshold (Ct) values. Meanwhile, PCR testing capacity needs urgent scale-up in LMICs and improved POC diagnostics are needed to facilitate COVID-19 diagnosis in LMICs.

Table 1: Overall Sensitivity, Specificity, PPV and NPV - PCR as the Gold standard*

| POINT OF CARE ANTIGEN TESTS | Sensitivity (95%CI) | Specificity (95%CI) | PPV (95%CI) | NPV (95%CI) |
|---|---|---|---|---|
| **RapiGEN Inc. BIOCREDIT COVID-19 Antigen** (n=279) | 34.8 (26.1 – 44.2) | 97.6 (93.9 – 99.3) | 90.9 (78.3 – 97.5) | 68.1 (61.7 – 74.0) |
| **SD Biosensor STANDARDTM Q COVID-19** Antigen (n=784) | 49.1 (43.3 – 55.0) | 95.7 (93.5 – 97.3) | 87.3 (81.2 – 91.9) | 75.9 (72.4 – 79.2) |
| **LumiraDx COVID-19 Antigen** (n=757) | 63.8 (55.9 –71.2) | 97.0 (95.5 – 98.3) | 86.0 (78.5 – 91.6) | 90.7 (88.2 – 92.9) |

***Some figures may change as analysis is ongoing**

## 824 POINT-OF-CARE ANTIBODY TESTS FOR COVID-19: FIELD-BASED PERFORMANCE, SOUTH AFRICA

**Ameena Goga**[1], Elizabeth S. Mayne[2], Kubashni Woeber[1], Simbarashe Takuva[3], Duduzile Nsibande[4], Molebogeng Lekalakala[2], Shameem Jaumdally[5], Portia Mutevedzi[6], Helena Vreede[7], Brodie Daniels[4], Clement Kufe[2], Keertan Dheda[5], Kamy Chetty[2], Glenda E. Gray[1]

[1]South African Medical Research Council, Cape Town, South Africa, [2]National Health Laboratory Service, Johannesburg, South Africa, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [4]South African Medical Research Council, Durban, South Africa, [5]University of Cape Town, Cape Town, South Africa, [6]University of Witwatersrand, Johannesburg, South Africa, [7]National Health Laboratory Service, Cape Town, South Africa

**Background:** SARS-CoV2 antibody testing is an important auxillary test especially for retrospective diagnosis or in patients with long COVID-19 or multisystem inflammatory syndrome of childhood. Epidemiological serology studies may also assist public health planning. Access to formal laboratory testing is not universal in many low-and middle-income (LMIC) countries and rapid lateral flow antibody tests are an attractive alternative. Performance of these tests has been inconsistent. A large-scale study was undertaken in South Africa, during the beta and delta waves, to assess the field-based performance of rapid point of care (POC) COVID-19 antibody tests.

**Methods:** Symptomatic, ambulatory persons under investigation (PUIs) aged 18 years and older, presenting for SARS-CoV-2 diagnosis at public health facilities in three provinces, South Africa were enrolled at baseline. All patients completed a questionnaire regarding symptoms. Nasopharyngeal swabs were taken and processed for SARS-CoV-2 PCR testing using a GeneXpert (Cepheid, USA), or manual assay (ThermoFisher TaqPath assay or Seegene Allplex assay) on a real-time platform at routine accredited National Health Laboratory Service laboratories as per routine national protocols. Concomitantly, trained study staff performed three facility-based POC lateral flow antibody tests on a on a fingerstick sample and blood was collected for formal serology. POC tests were selected following a rapid in-laboratory evaluation. Asymptomatic contacts of people with confirmed COVID-19 were recruited into the asymptomatic study arm and rapid tests and PCR were performed. PCR and rapid positive patients and 500 negative controls were followed up at 5-14 days. Antibody tests were compared with formal serology performed on 2 platforms – Euroimmun (Euroimmun, Lubeck) IgA and IgG anti-S antibodies and Abbott Architect IgG test.

**Results:** The sensitivity (S), specificity (Sp), positive (PPV) and negative predictive (NPV) values of tests for PUIs and contacts were calculated (Table 1)*. Analyses using serology as a reference are forthcoming.

**Conclusion:** Compared with PCR, performance of rapid POC COVID-19 antibody tests was poor with low sensitivity. This may reflect the patient cohort tested as humoral responses typically develop from day 7-14. The tests are unlikely to be useful for acute diagnosis but sensitivity may improve at later timepoints and further follow up data will be analysed by duration of symptom onset, severity of symptoms and wave (beta versus delta).

**Table 1: Performance of antibody tests using PCR as a reference***

| POINT OF CARE ANTIBODY TESTS | Sensitivity (95%CI) | Specificity (95%CI) | PPV (95%CI) | NPV (95%CI) |
|---|---|---|---|---|
| **BIOSYNEX COVID-19 BSS Baseline: IgM/IgG** (n=1417) | 24.7 (20.5 – 29.3) | 85.1 (82.8 – 87.3) | 38.6 (32.5 – 44.9) | 75.0 (72.4 – 77.5) |
| **BIOSYNEX COVID-19 BSS Follow-up: IgM/IgG** (n=215) | 54.2 (32.8 – 74.4) | 81.2 (74.9 – 86.4) | 26.5 (14.9 – 41.1) | 93.4 (88.5 – 96.6) |
| **Genrui Biotech Novel Coronavirus (2019-nCoV) IgG/IgM Test Kit (Colloidal Gold) Baseline** (n=1088) | 22.6 (17.7 – 28.2) | 89.5 (85.0 – 89.7) | 37.8 (29.4 – 44.7) | 77.8 (75.0 – 80.5) |
| **Genrui Biotech Novel Coronavirus (2019-nCoV) IgG/IgM Test Kit (Colloidal Gold) Follow-up** (n=190) | 50.0 (27.2 – 72.8) | 88.2 (82.4 – 92.7) | 33.3 (17.3 – 52.8) | 93.8 (88.8 – 97.0) |
| Orient Gene Covid-19 Rapid antibody test **Baseline IgM/IgG** | 22.0 (17.9 – 26.5) | 84.4 (81.9 – 86.6) | 35.0 (29.0 – 41.4) | 73.8 (71.2 – 76.4) |
| Orient Gene Covid-19 Rapid antibody test **Follow-up IgM/IgG** (n=1 379) | 37.5 (18.8 – 59.4) | 76.1 (69.3 – 82.0) | 16.7 (7.9 – 29.3) | 90.5 (84.8 – 94.6) |

*Some figures may change as analysis is ongoing

## 825 PERFORMANCE OF SARS-CoV-2 ANTIBODY ASSAYS IN A NATIONAL SEROSURVEY IN SOUTH AFRICA

**Sizulu Moyo**[1], Adrian Puren[2], Leickness C. Simbayi[1], Khangelani Zuma[1], Nompumelelo Zungu[1], Mirriam Fortuin[2], Zinhle Brukwe[2], Beverley Singh[2], Tarylee Reddy[3], Edmore Marinda[1], Sean Jooste[1], Penny Moore[2], Lynn Morris[2], Thomas Rehle[4]

*[1]Human Sciences Research Council, Pretoria, South Africa, [2]National Institute for Communicable Diseases, Johannesburg, South Africa, [3]South African Medical Research Council, Durban, South Africa, [4]University of Cape Town, Cape Town, South Africa*

**Background:** Accurate and reliable serological assays are essential for epidemiological surveillance of SARS-CoV-2. Several commercial anti-SARS assays are available and use cases for serological testing includes surveillance. However, there is growing evidence of varying performance of SARS-CoV-2 assays dependent of their format. We compare the performance of 3 different assays used in a national serosurvey undertaken between April and June 2021, in South Africa before widescale vaccination roll out.

**Methods:** Venous blood samples from participants ≥12 years were transported under cold chain to a central testing laboratory within 24 hours of collection. Samples were tested for SARS CoV-2 antibodies with the Abbott nucleocapsid (NC)-based Architect anti-SARS CoV-2 chemiluminescent microparticle immunoassay (CMIA), the EuroImmun Spike (S)-based assay and the Roche total IgG NC-based Elecsys Anti-SARS-CoV-2 electrochemiluminescence immunoassay (ECLIA) on the Cobas e411 platform. We compared antibody detection proportions.

**Results:** 8146 participants (median age 40 years, IQR 26-55) 5.6% of whom reported ≥1 SARS-CoV-2 symptom in the preceding 3 months gave a blood sample. Samples were tested on the Abbott assay with different cut-offs:-15.5% tested positive at the 1.40 cut-off and 26.8% at the 0.49 lower cut-off. 21.6% of the samples tested positive on the Euroimmun and 39.0% tested positive on the Roche assay (Table). 286 samples were from respondents self-reporting a prior positive PCR test, and among them 149(52.1%), 156(54.6%), and 206(72.3%) were positive on the Abbott (1.40 cut-off), Euroimmun and Roche assays respectively. 116/286(40.6%) of these were positive on all three assays and with 21(7.3%) positive on Roche only. 224/286(78.3%) of those reporting prior PCR test positivity were positive at the lower Abbott cut-off, with 47(16.4%) positive on Abbott only.

**Conclusion:** These samples collected before wide scale vaccination roll out in South Africa show variable performance of these assays with the Roche NC assay detecting more infections that both the Abbott NC assay(0.40 cut-off) and the Euroimmun S assay.This could be reflective of seroreversion previously reported with Abbott and Euroimmun, and the greater sensitivity of Roche assay targeting the more abundant NC as an epitope. Use of direct, double Antigen-sandwich-based assays that are stable and have increased sensitivity over time may be optimal to detect both natural and vaccine-induced immunity in serosurveys.

**Table: Sample positivity by assay: SARS-CoV-2 household serosurvey in South Africa**

| Assay | Manufacturer | Method | Antibody | Antigen | Cut-off | Tested n | Positive n (%) |
|---|---|---|---|---|---|---|---|
| Abbott | Abbott Ireland Diagnostic Division | CMIA (Chemilumiscent Microplate) | IgG | *NC | ≥1.40 | 7816 | 1213 (15.5) |
| Abbott | Abbott Ireland Diagnostic Division | CMIA (Chemilumiscent Microplate) | IgG | *NC | 0.40 | 7816 | 2094 (26.8) |
| Euroimmun Anti-SARS-CoV-2 ELISA (IgG) | Euroimmun Medizinische Labordiagnosika AG | ELISA | IgG | **S | 0.8-1.1 | 7755 | 1677 (21.6) |
| Roche Elecsys Anti-SARS-CoV-2 | Roche Diagnostics GmbH | ECLIA (Electrochemiluminescence immunoassay | IgG Total | *NC | ≥1.0 | 7813 | 3050 (39,0) |

*Nucleocapsid
**Spike

## 826 PRE-PANDEMIC SARS-CoV-2 SEROPOSITIVITY AMONG PREGNANT WOMEN – ZAMBIA, 2017-2018

**Mpanji Siwingwa**[1], Jonas Hines[2], Sombo Fwoloshi[3], Samuel Yingst[2], Peter Minchella[2], Adam Wolkon[2], Gershom Chongwe[4], Simon Agolory[2], Lloyd B. Mulenga[3]

*[1]University Teaching Hospital, Lusaka, Zambia, [2]Centers for Disease Control and Prevention, Lusaka, Zambia, [3]Government of Zambia Ministry of Health, Lusaka, Zambia, [4]Tropical Diseases Research Centre, Ndola, Zambia*

**Background:** Reliable serologic assays are needed to accurately measure prevalence of prior exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, several countries in Africa have reported apparent SARS-CoV-2 assay cross-reactivity with other non-coronavirus pathogens. We used 3 SARS-CoV-2 serologic assays to assess positivity in archived serum specimens collected in Zambia prior to the COVID-19 pandemic and explored seropositivity associations with participant characteristics.

**Methods:** SARS-CoV-2 antibody seropositivity was measured using serum specimens collected from pregnant women aged 15-49 years enrolled in an HIV and syphilis sentinel surveillance study in 26 sites across Zambia during 2017-2018. Of 9,508 participants with archived specimens, 1,500 (16%) were selected using stratified random sampling (by study site). SARS-CoV-2 antibody seroprevalence was measured using the Panbio IgM/IgG lateral flow assay, Euroimmun spike IgG enzyme-linked immunosorbent assay (ELISA), and the Wantai pan-Ig ELISA. HIV and syphilis testing followed the national testing algorithms. We compared age group and HIV and syphilis status with SARS-CoV-2 antibody seropositivity using chi-square test.

**Results:** Among the 1,500 female participants, 1,297 (86%) had specimens available for testing. Participants' median age was 25 years (interquartile range: 21-30 years). HIV and syphilis prevalence were 16% and 6%, respectively. SARS-CoV-2 antibody seropositivity was 14% on the Panbio assay, 7% on the Euroimmun assay, and 2% on the Wantai assay. There was no concordance of positive results between the 3 assays, and no association between SARS-CoV-2 antibody seropositivity and age group, HIV status, or syphilis status on all 3 assays ($p>0.05$ for all comparisons).

**Conclusion:** Three SARS-CoV-2 serologic assays showed antibody positivity in pre-pandemic specimens, possibly indicating cross-reactivity with antibodies to other coronaviruses or other non-coronavirus pathogens. Panbio and Euroimmun assays yielded more false positives than would be expected based on manufacturer-reported specificities. Although there was no association of SARS-CoV-2 antibody seropositivity with HIV or syphilis, testing for other pathogens could provide information about the identities of cross-reacting antibodies with these assays. Assessing for virus neutralizing capability of cross-reacting antibodies in SARS-Cov-2 antibody positive specimens could provide information about possible pre-existing SARS-CoV-2 immunity.

## 827 SARS-CoV-2 RAPID ANTIGEN DIAGNOSTICS: COMBINED ANALYSIS OF 8 MATHEMATICAL MODELS

**Karla Therese L. Sy**[1], Joshua M. Chevalier[1], Alvin X. Han[2], Sarah J. Girdwood[3], Mariet Benade[1], Megan Hansen[1], Naushin Huq[4], Amy Toporowski[4], Anna Bershteyn[5], Colin A. Russell[2], Brooke Nichols[1]
*[1]Boston University, Boston, MA, USA, [2]Amsterdam University Medical Center, Amsterdam, Netherlands, [3]University of Witwatersrand, Johannesburg, South Africa, [4]Foundation for Innovative New Diagnostics, Geneva, Switzerland, [5]New York University, New York, NY, USA*

**Background:** Antigen-detecting rapid diagnostic tests (Ag-RDT) for SARS-CoV-2 are an inexpensive diagnostic tool with fast turnaround times. Ag-RDTs in combination with measures to reduce contact rates after a positive test result can reduce the spread of SARS-CoV-2. Understanding when and in what settings Ag-RDTs can best be utilized to reduce transmission is critical for resource allocation. Here, we used a suite of mathematical models to quantify the impact of SARS-CoV-2 Ag-RDT testing strategies on COVID-19 outcomes in a variety of use-cases.
**Methods:** Our analysis synthesized the results from eight mathematical models from different modeling groups to assess the potential impact of Ag-RDT testing for SARS-CoV-2 infection across multiple use cases: (a) community testing, (b) mass gatherings, (c) K-12 schools (kindergarten to 12th grade/high school, or primary/secondary education), (d) universities, (e) border crossings, and (f) testing to exit quarantine. We calculated two outcomes relative to the status quo in each use case: (1) impact: the percent and number of infections averted and (2) efficiency: the number of tests required to avert one infection. We investigated the impact of different epidemic conditions including effective reproductive number (Rt) and COVID-19 prevalence, and the frequency of testing (for community testing, K-12 schools, and universities).
**Results:** Different use cases require varying testing strategies to reduce infections most efficiently and effectively across a range of epidemic conditions, with some global trends. Overall, there were tradeoffs with impact and efficiency. Across use cases, increasing test frequency (and/or more testing) was associated with greater percentage of infections averted. However, lower testing frequency was generally more efficient. In the community testing and university use cases, testing was most effective and efficient when Rt and/or infection prevalence was low but for border crossings testing was most effective and efficient when Rt and/or infection prevalence were high (Table 1).
**Conclusion:** The optimal timing of the intervention depends on whether one is trying to maximize effectiveness or efficiency, and on the use case itself. For a robust understanding of total community-level impact and cost-effectiveness, future work should aim to assess the combined impact of interventions through a single model that can consider all use-cases.

**Table 1. Summary of the general trends for each use case**

| Use case | Most impactful (effective) scenarios | | | | | Most efficient scenarios | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Rt | Prevalence | Test frequency | Other parameter | Other parameter | Rt | Prevalence | Test frequency | Other parameter | Other parameter |
| Community testing | Low (0.8) | Low (0.1%) | High (2x a week) | Test effectiveness – high (80%) | Proportion tested – high (90%) | Low (0.8) | Low (0.1%) | Moderate (1x a week) | Test effectiveness – high (80%) | Proportion tested – low (2.5%) |
| Mass gathering | | Similar for all | | Duration of event – short | Timing of test – day of event | | | | | |
| K-12 | High (2) | Low (0.1%) | High (2x a week) | Groups tested – testing all teachers and all pupils | | High (2) | High (1%) | Low (1x every 2 weeks) | Groups tested – testing all pupils aged 13-18 | |
| University | Low (0.8) | Low (0.1%) | High (2x a week) | | | Low (0.8) | Low (0.1%) | Low (1x every 2 weeks) | | |
| Border crossings (ASTAR, BUSPH, LSHTM) | | High (2%) | Negative PCR + Ag-RDT at border | | | | High (2%) | Ag-RDT at the border only | | |
| Exiting quarantine | | Exposed prevalence – similar for all | Daily testing strategy<br>Days with daily testing – high (10 days) | Delay to contact tracing – low (0 days) | Days in quarantine – high (10 days)<br>Days in isolation – low (3 days) | | Exposed prevalence – high (50%) | Test to release testing strategy<br>Days with daily testing - low (3 days) | Delay to contact tracing – low (0 days) | Days in quarantine – moderate (5 days)<br>Days in isolation – low (3 days) |

## 828 ESTIMATION OF SARS-CoV-2 CUMULATIVE INCIDENCE: AN APPLICATION OF MIXTURE MODELING

**Rifa Khan**[1], Matt Hitchings[2], Eshan U. Patel[3], Aylur K. Srikrishnan[4], Mark Anderson[5], K. S. Kumar[1], Amy Wesolowski[3], Syed H. Iqbal[1], Mary A. Rodgers[5], Shruti H. Mehta[3], Gavin Cloherty[5], Derek A. Cummings[2], Sunil S. Solomon[3]
*[1]YR Gaitonde Centre for AIDS Research and Education, Chennai, India, [2]University of Florida, Gainesville, FL, USA, [3]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [4]Aalborg University Hospital, Aalborg, Denmark, [5]Abbott Labs, Abbott Park, IL, USA*

**Background:** With global vaccine scale-up, the utility of the more stable anti-S IgG assay in seroprevalence studies is limited. P population prevalence estimates of anti-N IgG SARS-CoV-2 using alternate targets (eg, anti-N IgG) will be critical for monitoring cumulative SARS-CoV-2 incidence., We demonstrate the utility of a Bayesian approach that accounts for heterogeneities in SARS-CoV-2 seroresponse (eg, must consider mild infections and/or antibody waning) to ensure anti-N IgG prevalence is not underestimated and correlates not misinterpreted.
**Methods:** We sampled 4,828 participants from 2,723 households across 100 unique geospatial locations in Chennai, India, from Jan-May, 2021 when <1% of the general population was vaccinated. All samples were tested for SARS-CoV-2 IgG antibodies to S and N using the Abbott ARCHITECT. We calculated prevalence using manufacturer cut-offs and applied a Bayesian mixture model. In the mixture model, individuals were assigned a probability of being seropositive or seronegative based on their normalized index value, accounting for differential immune response by age and antibody waning. Regression analyses to identify correlates of infection defined seropositivity by manufacturer cut-offs and the mixture model.
**Results:** The raw SARS-CoV-2 seroprevalence using IgG to S (cutoff=50) and N (cutoff=1.4) were 61.9% (95% confidence interval [CI]: 60.5-63.3%) and 13.7% (CI: 12.8-14.7%), respectively with a correlation of 0.33. With the mixture model, anti-N IgG prevalence was 65.4% (95% credible interval [CrI]: 61.8-68.9). Correlates of anti-N IgG positivity differed qualitatively by the two approaches (Table). Using the manufacturer cut-off, income loss during the pandemic, household crowding and lack of air conditioning were associated with significantly lower anti-N prevalence. By contrast, in the mixture model, many measures of lower socioeconomic status were associated with higher prevalence, associations that were comparable when anti-S was the outcome. The age pattern differed between approaches: the mixture model identified that individuals aged >50 had the lowest seroprevalence, but the highest immune response to infection.
**Conclusion:** With global vaccine scale-up, population prevalence estimates of anti-N IgG will be critical for monitoring cumulative SARS-CoV-2 incidence. We demonstrate the utility of a Bayesian approach that accounts for heterogeneities in SARS-CoV-2 seroresponse to improve accuracy of anti-N IgG prevalence estimates and associated correlates.

**Correlates of anti-N and anti-S seropositivity among 4798 individuals sampled across Chennai, India: Results from Standard Manufacturer Cut-off and Bayesian Mixture model approaches**

| | Anti-N IgG Manufacturer cut-off (>1.4) | | Anti-N IgG Bayesian Mixture model | | Anti-S IgG Manufacturer cut-off (>50) | |
|---|---|---|---|---|---|---|
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| Age (in years) | | | | | | |
| 5-17 | 0.97 (0.59-1.59) | 1.07 (0.65-1.75) | 1.65 (0.85,3.58) | 1.73 (0.74,4.44) | 0.82 (0.59-1.14) | 0.84 (0.61-1.17) |
| 18-29 | REF | REF | REF | REF | REF | REF |
| 30-39 | 1.54 (1.14-2.08) | 1.49 (1.11-2.01) | 1.09 (0.70,1.71) | 1.06 (0.60,1.86) | 1.07 (0.87-1.33) | 1.04 (0.84-1.29) |
| 40-49 | 1.99 (1.49-2.68) | 1.90 (1.42-2.55) | 0.90 (0.58,1.35) | 0.81 (0.47,1.37) | 1.18 (0.95-1.46) | 1.13 (0.91-1.40) |
| ≥50 | 2.28 (1.74-2.99) | 2.10 (1.60-2.77) | 0.52 (0.36,0.74) | 0.42 (0.25,0.68) | 1.11 (0.91-1.36) | 1.12 (0.91-1.37) |
| Gender | | | | | | |
| Female | REF | REF | REF | REF | REF | REF |
| Male | 0.79 (0.65-0.96) | 0.85 (0.70-1.03) | 0.67 (0.52,0.86) | 0.62 (0.45,0.85) | 0.69 (0.60-0.80) | 0.70 (0.60-0.81) |
| Transgender | 1.15 (0.19-6.78) | 1.38 (0.24-7.76) | 1.18 (0.06,101.1) | 0.62 (0.02,93.1) | 0.41 (0.10-1.69) | 0.36 (0.09-1.47) |
| Maximum household education | | | | | | |
| No formal education | REF | - | REF | - | REF | - |
| Standard 1-8 | 0.78 (0.37-1.67) | | 0.90 (0.30,2.29) | | 1.23 (0.69-2.19) | |
| 9th standard or more | 1.03 (0.50-2.13) | | 0.91 (0.31,2.28) | | 1.25 (0.72-2.18) | |
| Household income | | | | | | |
| No change/increase due to COVID-19 | REF | - | REF | - | REF | - |
| Negative COVID-19 impact | 0.68 (0.55-0.84) | | 1.10 (0.83,1.47) | | 0.91 (0.76-1.08) | |
| Household ventilation system | | | | | | |
| Neither coolers nor air conditioning | REF | REF | REF | REF | REF | REF |
| Coolers only | 0.97 (0.61-1.53) | 1.01 (0.64-1.61) | 1.16 (0.63,2.17) | 1.10 (0.52,2.42) | 0.98 (0.69-1.40) | 1.02 (0.71-1.46) |
| Air conditioning only | 1.73 (1.35-2.20) | 1.41 (1.07-1.87) | 0.66 (0.46,0.94) | 0.59 (0.38,0.92) | 0.93 (0.76-1.15) | 0.92 (0.73-1.17) |
| Air conditioning and cooling systems | 1.92 (1.16-3.17) | 1.43 (0.85-2.41) | 0.63 (0.32,1.21) | 0.51 (0.22,1.15) | 0.60 (0.38-0.94) | 0.64 (0.41-1.01) |
| Household crowding (person/rooms) | 0.85 (0.77-0.92) | 1.00 (0.91-1.10) | 1.75 (1.11,2.78) | 1.11 (0.93,1.32) | 1.03 (0.96-1.10) | 1.00 (0.92-1.08) |
| No. of regular visitors to home | 0.94 (0.87-1.02) | 0.94 (0.86-1.03) | 1.10 (0.98,1.24) | 1.14 (0.99,1.33) | 1.06 (0.99-1.13) | 1.09 (1.02-1.17) |

*Also adjusted for month of sample collection; anti-S model included 4705/4798 participants

## 829 DIFFERENCES IN SEXUAL HEALTH CLINIC SERVICES BY AGE AND GENDER IN METROPOLITAN BOSTON

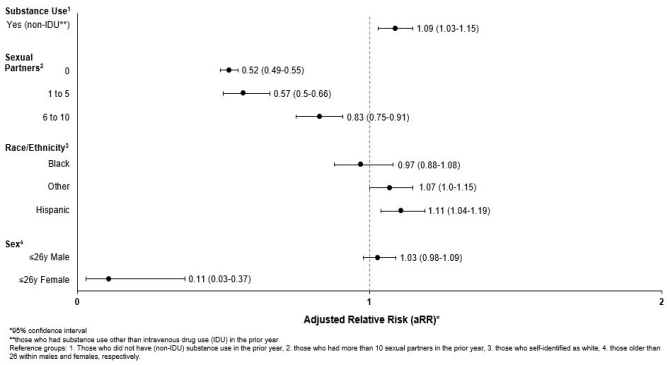
**Anne M. Neilan**[1], Yiqi Qian[1], Grace Chamberlin[1], Fatma M. Shebl[1], Kevin L. Ard[1]
*[1]Massachusetts General Hospital, Boston, MA, USA*

**Background:** Adolescents and young adults (AYA) seeking sexual health services may interact with healthcare differently than older adults due to multiple factors. HIV pre-exposure prophylaxis (PrEP) may be under-prescribed to AYA females.
**Methods:** Among clients of a Boston metropolitan sexual health clinic (01/2019-06/2021), we stratified outpatient visits, sexually transmitted infections (STI), PrEP use, and health insurance by age (15-22y, >22-26y, >26-45y, >45y) and gender. We assessed associations between age (≤26y vs. >26y) and current PrEP use among those with indications with multivariable Poisson regression. We estimated adjusted relative risk (aRR) and 95% confidence intervals (CI). We assessed interactions between gender and age and confounding by demo-economic factors.
**Results:** Among 4,005 patients, there were 7,953 visits (78% male; 50% white, 59% US born, 20% uninsured); 6% of visits led to a lab diagnosis of chlamydia,

3% gonorrhea, 2% syphilis, 0.2% new HIV, and 23% ≥1 STI. A PrEP indication was identified at 51 and 73% of visits attended by males and females; 5 and 9% had never heard of PrEP. A lab test was completed in 71%. Among those ages 15-22y, >22-26y, >26-45y, and >45y there were 302, 950, 2,175 and 578 visits. Demographics that increased by age (all p <0.0001) included proportion: male (64%, 69%, 81%, 89%), white (37%, 49%, 49%, 67%), >10 sex partners in prior year (27%, 32%, 35%, 37%), and any transactional sex (<1%, 3%, 3%, 12%). The youngest ages (all p<0.0001) had the most uninsured (15-22y: 21%; >22-26y: 18%; >26-45y: 20%; >45y: 17%), non-injection drug use (18%, 17%, 15%, 7%), never heard of PrEP (11%, 9%, 8%, 6%), and the least composite HIV/STI positivity (1%, 0.2%, 2%, 5%). Of those with indications, 83% vs. 8% of males vs. females were current PrEP users. Comparing females ≤26y vs. >26y with a PrEP indication, 1 vs. 14% were current PrEP users; comparing males ≤26y vs. >26y with a PrEP indication, 85% vs. 82% were current PrEP users. In females, ≤26y vs. >26y was associated with 89% decrease in current PrEP use among those with an indication; whereas in males, the association was not significant (Figure). Race, sexual partners, and substance use also predicted current PrEP use.

**Conclusion:** In a metropolitan sexual health clinic, we identified key differences in care by age and gender. Younger female age groups with a PrEP indication were least likely to be prescribed PrEP, reflecting opportunities to increase use of preventive resources.

Predictors of Current PrEP Use Among Visits with PrEP Indication




*95% confidence interval
**those who had substance use other than intravenous drug use (IDU) in the prior year
Reference groups: 1. Those who did not have (non-IDU) substance use in the prior year, 2. those who had more than 10 sexual partners in the prior year, 3. those who self-identified as white, 4. those older than 26 within males and females, respectively.

## 830 ASSESSING THE BENEFITS OF PREVENTION VERSUS CARE CONTINUUM INTERVENTIONS IN BALTIMORE

**Melissa Schnure**[1], Parastu Kasaie[1], David Dowdy[1], Maunank Shah[2], Ruchita Balasubramanian[1], Anthony T. Fojo[2]
*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** The United States' Ending the HIV Epidemic initiative seeks to reduce new HIV infections over the next decade through improved diagnosis, treatment, and prevention. Intermediate steps along the HIV continuum of care play a key role in achieving the initiative's goals; the impact of interventions on the continuum relative to prevention efforts is unclear.

**Methods:** We adapted the Johns Hopkins Epidemiological and Economic Model, a dynamic model of HIV epidemics in US cities, to quantify the benefits of improved pre-exposure prophylaxis (PrEP) coverage, linkage, retention, and suppression among key risk groups in Baltimore, MD. We compared scenarios with improved PrEP coverage (proportion at risk for HIV infection who are enrolled in a PrEP program); linkage (proportion of people with HIV [PWH] linked to care within three months of diagnosis); retention (proportion of PWH in care who remain engaged in care), and suppression (proportion of unsuppressed individuals who achieve viral suppression). Interventions were scaled up from 2023-2027 in three groups: young (age <35) Black and Hispanic men who have sex with men (MSM); all MSM and people who inject drugs (PWID); and the full population of the city. Our primary outcome was reduction in HIV incidence from 2020 to 2030, evaluated as the mean across 200 independent model simulations.

**Results:** Of the interventions considered, those that had greatest impact were expansion of PrEP coverage to 25% and increasing retention in care to 95% per year. When targeting young Black and Hispanic MSM, improving PrEP coverage to 25% reduced ten-year HIV incidence by a projected 51%, while improving retention in care to 95% (with stable PrEP coverage) provided an estimated 47% reduction (Table). Expanding 25% PrEP coverage to all MSM and PWID resulted in an estimated 54% reduction in incidence, whereas expanding 95% retention in care resulted in an estimated 57% reduction. Considering the full population, 25% PrEP coverage and 95% retention were similarly impactful, reducing ten-year incidence by 63% and 61%, respectively. The maximum possible impact was achieved by targeting the full population in a combination intervention of 25% PrEP coverage, 95% linkage, 95% retention, and 95% suppression, which achieved an estimated 77% reduction in ten-year incidence.

**Conclusion: Improvements** in PrEP coverage and retention among key risk groups yield large incidence reductions in Baltimore and will be key to achieving EHE goals.

**Table:** Ten-year reduction in HIV incidence in Baltimore-Columbia-Towson, MD Metropolitan Statistical Area. Values represent the percent reduction in incidence across the entire MSA population, given select risk group interventions. (Combined (low): 10% PrEP + 90% linkage + 90% retention + 90% suppression; Combined (high): 25% PrEP + 95% linkage + 95% retention + 95% suppression)

| | No int | PrEP | | Linkage | | Retention | | Suppression | | Combined (low) | Combined (high) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 10% | 25% | 90% | 95% | 90% | 95% | 90% | 95% | | |
| Black/Hispanic MSM <35 | 44% | 45% | 51% | 44% | 44% | 45% | 47% | 45% | 45% | 46% | 54% |
| All MSM, All PWID | | 43% | 54% | 44% | 45% | 48% | 57% | 46% | 48% | 48% | 65% |
| Full city population | | 49% | 63% | 44% | 45% | 49% | 61% | 47% | 50% | 56% | 77% |

## 831 COST-EFFECTIVENESS OF HIV PrEP AMONG YOUNG MEN WHO HAVE SEX WITH MEN IN THE US

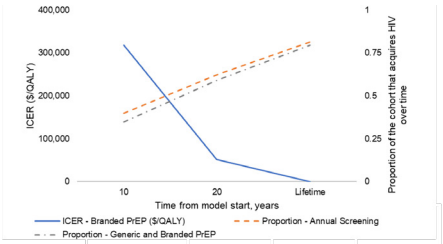
**Alyssa K. Amick**[1], G. Ege Eskibozkurt[1], Sybil Hosek[2], Clare Flanagan[1], Raphael J. Landovitz[3], Kenneth Freedberg[1], Craig M. Wilson[4], Milton C. Weinstein[5], David Paltiel[6], Andrea Ciaranello[1], Anne M. Neilan[1]
*[1]Massachusetts General Hospital, Boston, MA, USA, [2]Stroger Hospital of Cook County, Chicago, IL, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]University of Alabama at Birmingham, Birmingham, AL, USA, [5]Harvard TH Chan School of Public Health, Boston, MA, USA, [6]Yale University, New Haven, CT, USA*

**Background:** Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) studies 110/113 found oral tenofovir disoproxil fumarate/emtricitabine (F/TDF) HIV pre-exposure prophylaxis (PrEP) to be safe and feasible among young men who have sex with men (YMSM, ages 13-24). However, questions remain about the cost-effectiveness of PrEP in this population with low adherence and retention.

**Methods:** We used a simulation model to compare annual HIV screening alone to PrEP with quarterly screening among YMSM at high risk of HIV acquisition. Data derived from published sources included: age-stratified HIV incidence/100PY [off-PrEP (15-17y: 10.2, 18-34y: 5.2, 35-44y: 5.0, 45-54y: 3.2, ≥55y: 0.7); on-PrEP (15-17y: 6.5, 18-34y: 3.3, 35-44y: 3.1, 45-54y: 2.0, ≥55y: 0.5]) and PrEP retention at 10 years (11%). We stratified primary onward HIV transmissions by HIV RNA level (0.0-78.4/100PY). Annual costs included antiretroviral therapy (ART, $31,000), HIV care ($300-$1,200), and PrEP program and drug ($430+$360). Projected outcomes included HIV transmissions, quality-adjusted life years (QALY), costs, and incremental cost-effectiveness ratios (ICER, $/QALY) over 10-year, 20-year, and lifetime horizons. We explored the sensitivity of our findings to annual costs of branded PrEP drug ($9,100) and ART ($0-$47,500), and HIV incidence (as low as 0.01/100PY, i.e., general population including those not meeting PrEP eligibility criteria).

**Results:** Compared to annual screening, PrEP would increase QALYs (8.37 to 8.42), reduce new HIV infections (40% to 35%), and decrease costs (by $14,000) over 10 years among YMSM at high-risk of HIV infection. At a 10-year horizon, PrEP would be cost saving at HIV incidences off-PrEP ≥0.2/100PY and ART cost ≥$1,200. At the lifetime horizon, PrEP would be cost saving even if ART were free or if HIV incidence off-PrEP were ≥0.4/100PY. At incidences as low as 0.01/100PY, the ICER would be $600,000/QALY over a lifetime. With branded PrEP drug price, PrEP would increase costs by $15,000 over a 10-year horizon resulting in an ICER of $347,000/QALY ($51,000/QALY over 20 years); at this price point, PrEP would be cost saving over a lifetime horizon.

**Conclusion:** In a population of US YMSM at high risk of HIV acquisition, PrEP compared to annual HIV screening alone would be cost saving, despite high discontinuation rates and poor adherence. At generic PrEP prices, PrEP would be cost saving over a lifetime even with free ART or HIV incidences lower than observed among YMSM in ATN 110/113.




| | Time horizon | Strategy | QALY, per person | Cost, per person | ICER*, $/QALY |
|---|---|---|---|---|---|
| Generic PrEP price[a] | 10 years | PrEP | 8.42 | 31,000 | - |
| | | Annual Screening | 8.37 | 45,000 | Dominated |
| | 20 years | PrEP | 14.09 | 91,000 | - |
| | | Annual Screening | 14.04 | 118,000 | Dominated |
| | Lifetime | PrEP | 22.93 | 270,000 | - |
| | | Annual Screening | 22.89 | 305,000 | Dominated |
| Branded PrEP price | 10 years | Annual Screening | 8.37 | 45,000 | - |
| | | PrEP | 8.42 | 60,000 | 318,000 |
| | 20 years | Annual Screening | 14.04 | 118,000 | - |
| | | PrEP | 14.09 | 121,000 | 51,000 |
| | Lifetime | PrEP | 22.93 | 300,000 | - |
| | | Annual Screening | 22.89 | 305,000 | Dominated |

Abbreviations: $, 2020 US dollars; ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.
*Incremental cost-effectiveness ratios are the difference in total healthcare-related costs divided by the difference in total QALYs compared to the next most expensive strategy. Costs and QALYs are discounted at 3%/year.
[a]Generic PrEP is not graphed as it would be cost saving compared to generic F/TDF.
Strategies are listed in order of increasing cost per cost-effectiveness analysis convention. Dominated strategies are more expensive and less effective than another strategy.

## 832 OUT-OF-POCKET PAYMENTS FOR PrEP DRUGS DECREASED ONLY MODESTLY IN 2021

**Ya-Lin A. Huang**[1], Weiming Zhu[1], Karen W. Hoover[1]
[1]*Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** Under the Affordable Care Act (ACA), preventive services with an A rating from the U.S. Preventive Services Task Force must be covered by health plans without patient cost sharing, including PrEP medications. Starting January 2021, most health plans were required to offer PrEP to their beneficiaries without copays. The objective of this study was to monitor time trends in total and out-of-pocket (OOP) payments for PrEP medications before and after implementation of the ACA requirement for no cost sharing.
**Methods:** We analyzed IQVIA Real World Data-Longitudinal Prescriptions Database to identify PrEP prescriptions using a validated algorithm. We estimated mean total and OOP payment per 30 PrEP tablets from January 2019 through March 2021, stratified by payer type and drug type. Payer type included commercial insurance, Medicaid, Medicare, cash payment, Gilead medication/copay assistance programs, and the federal Ready, Set, PrEP program. The three types of drugs currently available for PrEP are brand tenofovir disoproxil fumarate/emtricitabine (F/TDF), brand tenofovir alafenamide/emtricitabine (F/TAF; since October 2019), and generic F/TDF (since October 2020).
**Results:** We identified 2,216,789 PrEP prescriptions with complete payment data (71% of all PrEP prescriptions). In 2019, 95% of the PrEP tablets prescribed were F/TDF, and 5% F/TAF. The proportion of F/TAF tablets prescribed increased since 2019 to 40% in 2020, and 47% in Q1 2021. The proportion of generic F/TDF tablets prescribed increased from 7% in 2020 to 35% in Q1 2021. The mean OOP payment per 30 tablets for generic F/TDF was $13 in 2020, and $10 in Q1 2021. As a result, mean total payments per 30 tablets for PrEP drugs decreased from $1,687 in 2020 to $1,581 in January-March 2021 due to more use of generic PrEP. When stratified by payer type, the mean OOP payment per 30 tablets among those with commercial insurance decreased from $108 in 2019 to $97 in Q1 2020. Mean OOP payment per 30 tablets among cash payers decreased from $1,762 in 2019 to $1,346 in Q1 2021 (Table).
**Conclusion:** We observed only a modest decreasing trend in OOP payments for PrEP in Q1 2021; and the decrease was largely due to persons with commercial insurance and cash payers. The ACA provision for no patient cost sharing can increase access to PrEP by removing financial barriers. Ongoing monitoring of trends in PrEP drug payments is important to understand impact of the ACA policy as the proportion of persons in grandfathered, exempt plans decreases.

**Table. Number of PrEP prescriptions, tablets, and payments represented in the IQVIA database, January 2019 – March 2021**

| | 2019 | 2020 | Q1 2021 |
|---|---|---|---|
| PrEP users*, n | 183,384 | 212,185 | 137,167 |
| PrEP prescriptions*, n | 917,713 | 1,029,441 | 269,635 |
| PrEP tablets*, n | 32,702,021 | 36,575,226 | 9,848,867 |
| F/TDF, n (%) | 31,074,624 (95%) | 19,314,906 (53%) | 1,805,965 (18%) |
| F/TAF, n (%) | 1,627,397 (5%) | 14,779,546 (40%) | 4,582,610 (47%) |
| Generic F/TDF, n (%) | NA | 2,480,774 (7%) | 3,460,292 (35%) |
| Mean total payments per 30 tablets, $ (SD) | 1,644 (304) | 1,687 (364) | 1,571 (492) |
| Mean OOP payments per 30 tablets, $ (SD) | 90 (239) | 85 (250) | 84 (305) |
| Drug type | | | |
| F/TDF | 92 (239) | 86 (255) | 88 (323) |
| F/TAF | 86 (228) | 96 (257) | 137 (367) |
| Generic F/TDF | NA | 13 (105) | 10 (117) |
| Payer type | | | |
| Commercial | 108 (248) | 103 (257) | 97 (321) |
| Medicaid | 2 (38) | 4 (70) | 6 (99) |
| Medicare | 83 (190) | 99 (225) | 177 (310) |
| Cash | 1,762 (703) | 1,724 (922) | 1,346 (970) |
| Gilead MAP | 1 (40) | 5 (96) | 19 (190) |
| Ready, Set, PrEP | NA | 4 (92) | 0 (0) |

Note: Q1=first quarter from January to March; F/TDF=tenofovir disoproxil fumarate and emtricitabine; F/TAF=tenofovir alafenamide and emtricitabine; OOP=out-of-pocket; MAP=medication assistance program; SD=standard deviation; NA=not applicable.
*Based on PrEP prescriptions with complete payment data in the IQVIA database.

## 833 PRESCRIPTIONS FOR BRAND AND GENERIC PrEP MEDICATIONS IN THE UNITED STATES

**Duygu Islek**[1], Weiming Zhu[1], Ya-Lin A. Huang[1], Karen W. Hoover[1]
[1]*Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** Emtricitabine and tenofovir disoproxil fumarate (F/TDF) and emtricitabine and tenofovir alafenamide (F/TAF) are safe and effective drugs for PrEP, however the costs of these drugs result in high expenditures in the U.S. healthcare system. Several generic formulations of F/TDF were approved by FDA in the fall of 2020. We estimated the prevalence of F/TDF, F/TAF and generic F/TDF prescriptions and their association with patient demographic factors in the United States.
**Methods:** We analyzed the IQVIA Real-World prescription database to estimate the number of persons aged ≥16 years who had at least one PrEP prescription for F/TDF, F/TAF, or generic F/TDF between October 1, 2020 and March 31, 2021. We identified persons prescribed PrEP using a previously validated algorithm and described the proportions of each drug type prescribed over time. We used multinomial logistic regression models to estimate the associations between drug prescribed for PrEP and patient demographic characteristics, including race/ethnicity information that was available for 35% of persons in the database.
**Results:** Among 240,409 persons prescribed PrEP during the study period, 44% were prescribed F/TAF, 33.3% generic F/TDF, and 22.3% F/TDF. The proportion of PrEP users prescribed F/TDF decreased from 36.5% in October 2020 to 18.8% in March 2021, and those prescribed generic F/TDF increased from 16.6% in October 2020 to 33.3% in March 2021. In multinomial models, the adjusted odd ratios (aORs) of being prescribed generic F/TDF vs. F/TDF and F/TAF vs. F/TDF in March 2021 were higher compared to prescriptions in October 2020 (aOR=4.04 (3.84-4.25) and aOR=2.80 (2.68- 2.91), respectively). Women were less likely to be prescribed F/TAF or generic F/TDF vs. F/TDF (Table). Compared to those with private insurance, persons who had public insurance or paid with cash were less likely to be prescribed F/TAF vs. F/TDF (aOR=0.67 (0.65-0.69) and aOR=0.84 (0.77-0.91), respectively) or generic F/TDF vs. F/TDF (aOR=0.51 (0.50-0.53) and aOR=0.72 (0.66- 0.78), respectively). Black and Hispanic persons were less likely to be prescribed generic F/TDF vs. F/TDF; however, they were more likely to be prescribed F/TAF vs. F/TDF compared to White persons (Table).
**Conclusion:** Generic F/TDF is a less expensive option for PrEP and was more likely to be prescribed than F/TDF, especially among persons with private insurance. Choice of less expensive PrEP prescriptions might help decrease the health care expenditure burden in the United States.

**Table:** Number of persons aged ≥16 years prescribed HIV preexposure prophylaxis by selected characteristics, IQVIA Prescription Database, United States, October 1, 2020–March 31, 2021

| Characteristic | Total, N | F/TDF, N (%) | F/TAF N (%) | Generic F/TDF, N (%) | F/TAF vs. F/TDF, a OR* (95% CI) | Generic F/TDF vs. F/TDF, aOR* (95% CI) |
|---|---|---|---|---|---|---|
| **Total** | 240,409 | 53,567 (22.3) | 106,684 (44.4) | 80,138 (33.3) | | |
| **Sex** | | | | | | |
| Male | 223,862 | 45,581 (20.4) | 103,717 (46.3) | 74.564 (33.3) | Reference | Reference |
| Female | 16,290 | 7,914 (48.6) | 2,857 (17.5) | 5,519 (33.9) | 0.17 (0.16 - 0.18) | 0.63 (0.61 - 0.66) |
| **Race/Ethnicity** | | | | | | |
| White | 56,196 | 11,333 (20.2) | 24,324 (43.3) | 20,539 (36.5) | Reference | Reference |
| Black | 11,910 | 2,884 (24.2) | 5,377 (45.1) | 3,649 (30.6) | 1.11 (1.05 - 1.17) | 0.92 (0.87 - 0.98) |
| Hispanic | 13,854 | 3,083 (22.3) | 6,815 (49.2) | 3,956 (28.6) | 1.14 (1.08 - 1.20) | 0.82 (0.78 - 0.87) |

*aOR=adjusted odds ratio; aORs were adjusted for sex, age, race/ethnicity, insurance type, and month using multinomial logistic regression models; unspecified race and sex groups were also included in the models

## 834 RURAL HIV PrEP USERS AND PROVIDERS IN THE UNITED STATES: 2014-2020

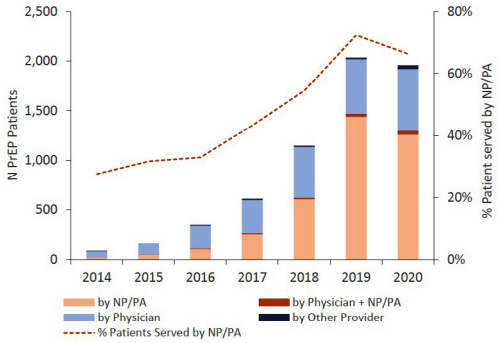
**Weiming Zhu**[1], Ya-Lin A. Huang[1], Athena Kourtis[1], Karen W. Hoover[1]
[1]*Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** One of the goals of the Ending the HIV Epidemic in the U.S. (EHE) initiative is to increase HIV preexposure prophylaxis (PrEP) use by persons at risk for acquiring HIV infection. The EHE priority jurisdictions include seven states with high numbers of HIV diagnoses in rural areas. Our objective was to estimate number of PrEP users and providers in these rural areas.

**Methods:** We analyzed 2014–2020 data from the IQVIA Real-World Longitudinal Prescriptions Database to identify persons who received a PrEP prescription based on a validated algorithm. We identified PrEP providers located in rural areas using providers' 5-digit zip codes and the Centers for Medicare and Medicaid Services locality files. We monitored time trends in the annual number of PrEP users; PrEP providers; and average number of PrEP users per provider and the estimated annual percentage change (EAPC) over time. We stratified by provider type (physicians, nurse practitioners, and physician assistants [NP/PA]).

**Results:** From 2014 to 2020, the number of rural PrEP users in the United States increased from 604 to 10,976 (EAPC 45.9%, 95%CI 45.1-46.8%). The number of rural PrEP users in EHE states increased from 87 to 1,957 (EAPC 58.7%, 95%CI 56.2-61.2%), and in non-EHE states from 517 to 9,021 users (EAPC 42.8%, 95%CI 41.9-43.7%). During the same time period, the number of rural PrEP providers in EHE states increased from 75 to 743 (EAPC 38.8%, 95%CI 35.5-41.7%). The number of NP/PA PrEP providers increased from 19 to 313 (EAPC 51.0%, 95%CI 45.5-56.6%), faster than the number of physicians (54 to 409, EAPC 32.2%, 95%CI 28.8-35.7%). In 2020, 55.0% of rural PrEP providers in EHE states were physicians, 42.1% were NP/PA, and 2.8% other types. More PrEP was prescribed by rural NP/PA than physicians. Of EHE rural PrEP users, 66.3% were served by NP/PA and 33.8% by physicians in 2020 (Figure). In EHE states, the average number of PrEP patients per NP/PA provider was 4.1, while that of physicians was 1.6.

**Conclusion:** The number of PrEP users and PrEP providers increased in EHE rural states more than in non-EHE states, likely because of EHE interventions focused on increasing HIV prevention in rural communities. In EHE states, NP/PAs comprised about 43% of providers and served more than two thirds of rural PrEP patients. Interventions can support rural PrEP providers as they prescribe PrEP, such as continuing education programs, enhanced PrEP training for new NP/PAs, and clinical decision support tools.




NP: Nurse Practitioner; PA: Physician Assistant

**Figure. PrEP users and PrEP prescriptions by provider type in Ending the HIV Epidemic in the U.S. initiative, rural states, United States, 2014–2020**

## 835 EFFECT OF NAVIGATION ON LINKAGE TO HIV PREEXPOSURE PROPHYLAXIS AMONG US MSM

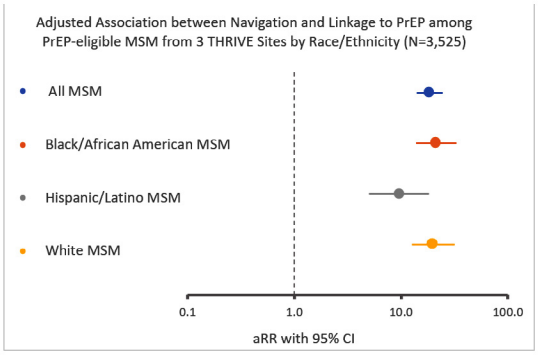
**Anne A. Kimball**[1], Weiming Zhu[1], Kashif Iqbal[1], Mary Tanner[1], Karen W. Hoover[1]
[1]*Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** Patient navigation improves linkage to and retention in HIV care for persons with HIV, but the benefits of navigation for pre-exposure prophylaxis (PrEP) uptake have not been well described. We evaluated the effects of navigation on linkage to a PrEP provider for men who have sex with men (MSM) who were eligible for PrEP in the THRIVE demonstration project. THRIVE funded 7 U.S. health departments to develop community collaboratives to provide HIV prevention and care services from 2015–2020, with a focus on Black/African American (Black) and Hispanic/Latino (Hispanic) MSM.

**Methods:** We described the number of MSM who were eligible for PrEP, linked to a PrEP provider, and used a PrEP navigator. MSM with unknown PrEP linkage were considered lost to follow up and not linked. We restricted our analysis to the 3 sites where navigation was optional and was the main PrEP support. We performed Poisson-regression modeling to evaluate the effect of navigation on PrEP linkage among eligible MSM, controlling for site, age group, and race/ethnicity. We stratified by race/ethnicity to evaluate the effect of navigation on PrEP linkage among Black, Hispanic, and White MSM.

**Results:** Among the 3,525 MSM eligible for PrEP from the 3 THRIVE sites included in this analysis, 21% linked to PrEP. By race/ethnicity, 18% of 1,704 eligible Black MSM linked to PrEP, 25% of 372 eligible Hispanic MSM linked to PrEP, and 21% of 1,256 eligible White MSM linked to PrEP. Among the 1,373 MSM who used navigation, 48% linked to PrEP. Overall, MSM who used navigation were 18.5 times as likely to link to PrEP than those who did not use navigation (95% CI 14.2-24.1), adjusting for site, age group, and race/ethnicity. Black MSM who used navigation were 21.4 times as likely to link to PrEP (95% CI 14.1-32.4), Hispanic MSM who used navigation were 9.6 times as likely to link to PrEP (95% CI 5.1-18.0), and White MSM who used navigation were 20.0 times as likely to link to PrEP (95% CI 12.8-31.3), than those who did not use navigation, adjusting for age group and site.

**Conclusion:** Navigation was a highly effective strategy for linking eligible MSM to a PrEP provider and was beneficial for Black, Hispanic, and White MSM. Navigation was less beneficial for Hispanic MSM in THRIVE compared with Black and White MSM, and further research is needed to understand facilitators and barriers to PrEP initiation for Hispanic MSM.




## 836 ESTIMATING BENEFITS FROM USING ON-DEMAND ORAL PrEP BY MSM IN US: A MODELING STUDY

New Investigator Scholar

**Sarah Stansfield**[1], Mia Moore[1], Marie-Claude Boily[2], James Hughes[3], Deborah Donnell[1], Dobromir Dimitrov[1]
[1]*Fred Hutchinson Cancer Research Center, Seattle, WA, USA,* [2]*Imperial College London, London, UK,* [3]*University of Washington, Seattle, WA, USA*

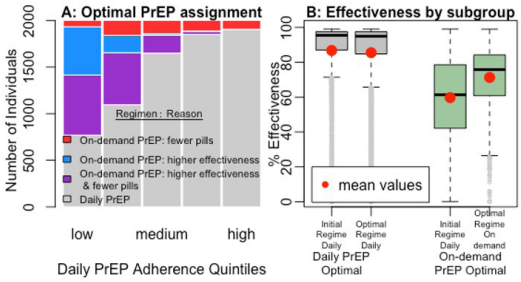
**Background:** Daily and on-demand pre-exposure prophylaxis (PrEP) with oral TDF-FTC are effective at preventing HIV acquisition among men who have sex with men (MSM), but only daily PrEP is recommended in the US. However, on-demand PrEP, in which individuals align their pill-taking with sexual activity, may improve uptake and adherence. In this modeling study, we aim to identify sub-groups of MSM who would benefit from using on-demand PrEP and determine the potential overall effectiveness achieved if individuals were assigned to their optimal regimen.

**Methods:** We simulated a cross-over trial in a synthetic cohort of 10,000 MSM whose pill taking and sexual behavior parameters were calibrated to data from the Harlem site of the HPTN 067 trial. Individuals were assigned daily PrEP for 6

months, followed by on-demand PrEP for 6 months (2-1-1 regime, with 2 pills the day of sex and 1 pill on each of the following 2 days). For each individual, we determined and assigned optimal regimen and simulated the whole cohort for another 6 months. Daily PrEP was the optimal regime unless on-demand PrEP had: i) improved effectiveness with fewer pills taken than daily PrEP in the initial simulations; ii) >10 percentage points (pp) higher effectiveness than daily PrEP with at most twice the number of pills taken, or iii) <10 pp lower effectiveness than daily PrEP with fewer than half the number of pills taken.

**Results:** On-demand PrEP was optimal and assigned mainly to MSM with low adherence to daily PrEP (62% of MSM in the lowest daily PrEP adherence quintile and only 5% of MSM in the highest). 78% of individuals for whom on-demand PrEP was optimal were from the lowest two daily PrEP adherence quintiles (panel A). The mean effectiveness for the full cohort when individuals used their optimal regimes was only 2 pp higher than universal daily PrEP use. However, for the subgroup for which on-demand PrEP was optimal (27% of the cohort), mean effectiveness was improved by 12 pp (panel B). There was little advantage to assigning on-demand PrEP by sex frequency, which was optimal for 28% and 25% of MSM in the lowest and highest sex frequency tertile, respectively.

**Conclusion:** On-demand PrEP could benefit many US MSM by increasing effectiveness or decreasing pill count with similar effectiveness. Most MSM for whom on-demand PrEP was optimal were in the lower daily adherence quintiles, indicating that on-demand PrEP should be offered to individuals with difficulty taking daily PrEP consistently.




*A: Optimal PrEP assignment by daily adherence quintile. Colors show reason for on-demand assignment. B: Effectiveness in daily PrEP optimal subgroup (in gray) or on-demand PrEP optimal subgroup (in green) in initial daily PrEP regime and in optimal regime.*

## 837 PrEP INDICATIONS AND PrEP KNOWLEDGE, ACCESS, AND INTEREST AMONG INDIVIDUALS WITH HCV

**Kristi C. Hill**[1], Rachel Silk[2], Rahwa Eyasu[2], Onyinyechi Ogbumbadiugha[2], Emade Ebah[2], Amelia A. Cover[2], Ashley Davis[2], David Sternberg[3], Phyllis Bijole[3], Junfeng Sun[4], Henry Masur[4], Shyam Kottilil[2], Sarah Kattakuzhy[2], Elana S. Rosenthal[2]
*[1]Harvard Medical School, Boston, MA, USA, [2]University of Maryland, Baltimore, MD, USA, [3]HIPS, Washington, DC, USA, [4]National Institutes of Health, Bethesda, MD, USA*

**Background:** Individuals with hepatitis C (HCV) represent a population who may benefit from PrEP, given overlapping risk factors and transmission networks of HCV and HIV. This analysis assesses the prevalence of PrEP indications among individuals with HCV and associations with PrEP awareness, access, and interest.

**Methods:** GRAVITY was an observational study for the collection of epidemiologic data from individuals with HCV and/or HIV, with the present analysis limited to HCV mono-infected patients. Participants were recruited from 7 sites in Washington DC and Baltimore. A drug use indication for PrEP was defined as injection drug use within 12 months and sharing of injecting equipment. A sexual indication for PrEP was defined as one of the following within 12 months: 1. >1 sexual partner and inconsistent condom use during anal or vaginal sex; 2. Transactional sex, defined as sex in exchange for drugs, money, or shelter; and/or 3. An HIV+ partner. Bivariate analysis assessed for associations between PrEP indications and PrEP awareness, access, and interest. Variables of significance were used to build a multivariable logistic regression model. Analyses were conducted using SAS version 9.3.

**Results:** Among 314 HCV mono-infected participants, 109 (35%) had an indication for PrEP. 48 (15%) had a drug use indication alone, 40 (13%) had a sexual indication alone, and 21 (7%) had both drug use and sexual indications. 85 (27%) participants had heard of PrEP, 32 (10%) had been offered PrEP by a provider, 114 (38%) were interested in PrEP, and 6 (2%) were currently taking PrEP. On bivariate analysis, PrEP awareness was significantly associated with study site (p<0.0001), race (p=0.0003), age (p<0.0001), and sexual (p=0.0373) PrEP indication. However, on regression analysis, only study site remained significant (p<0.0001). On regression analysis, past offer of PrEP by a provider was associated with study site (p=0.0012), and PrEP interest was associated with study site and self-perception of HIV risk (p=0.0028; p<0.0001).

**Conclusion:** Though indications for PrEP were prevalent among individuals with HCV in this cohort, most patients were unaware of PrEP, had never been offered PrEP, and were not using PrEP. The significant association between study site and both PrEP awareness and provider offerings of PrEP suggest high variability in PrEP access by location of healthcare utilization. These data support the need for improved PrEP implementation among people with HCV at risk for HIV acquisition.

**Table 1: Demographic Characteristics and Associations with PrEP Indications**

| | | Total (n,%) | Drug Use Indication (n,%) | | Sexual Indication (n,%) | |
|---|---|---|---|---|---|---|
| **Race** | *Black* | 275 (88) | 49 (18) | **p<.0001** | 40 (15) | **p<0.0001** |
| | *White* | 27 (9) | 17 (63) | | 15 (56) | |
| | *Other* | 12 (4) | 3 (25) | | 6 (50) | |
| **Gender** | *Female* | 105 (34) | 28 (27) | p>0.05 | 26 (25) | p>0.05 |
| | *Male* | 207 (66) | 41 (20) | | 33 (16) | |
| **Income** | *No income* | 133 (42) | 39 (29) | **p=0.005** | 32 (24) | p>0.05 |
| | *Has income* | 180 (58) | 29 (16) | | 29 (16) | |
| **Housing** | *Unstably housed* | 168 (54) | 42 (25) | p>0.05 | 38 (23) | p>0.05 |
| | *Stably housed* | 146 (47) | 27 (18) | | 23 (16) | |
| **Healthcare Access** | *No annual visits with PCP* | 115 (37) | 37 (32) | **p=0.0009** | 32 (28) | **p=0.0042** |
| | *Annual visits with PCP* | 199 (63) | 32 (16) | | 29 (15) | |

## 838 PrEP LONG-TERM ENGAGEMENT AMONG MSM AND TGW IN LATIN AMERICA: THE ImPrEP STUDY

**Valdilea Veloso**[1], Ronaldo I. Moreira[1], Kelika A. Konda[2], Brenda Hoagland[1], Hamid Vega-Ramirez[3], Iuri C. Leite[4], Juan V. Guanira[2], Sergio Bautista-Arredondo[5], Heleen Vermandere[5], Marcos R. Benedetti[1], Maria Pimenta[6], Thiago S. Torres[1], Beatriz Grinsztejn[1], Carlos F. Caceres[2]
*[1]Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, [2]Universidad Peruana Cayetano Heredia, Lima, Peru, [3]Instituto Nacional de Psiquiatria Ramón de la Fuente Muñiz, Mexico City, Mexico, [4]Escola Nacional de Saúde Pública, Rio de Janeiro, Brazil, [5]Instituto Nacional de Salud Pública, Mexico City, Mexico, [6]Ministério da Saúde, Brasília, Brazil*

**Background:** Although cisgender MSM (cis-MSM) and transgender women (TGW) suffer the highest burden due to the HIV epidemic in Latin America (LA), PrEP implementation is limited. ImPrEP was an implementation study to assess safety and feasibility of same-day PrEP initiation (daily-oral TDF/FTC) for cis-MSM and TGW vulnerable to HIV infection in Brazil, Peru and Mexico; results on factors associated with long-term PrEP engagement (LTPE) and HIV incidence are reported here.

**Methods:** Eligible cis-MSM and TWG (HIV-negative, ≥18 years- old, reporting 1+ risk criteria) were screened and enrolled on the same-day, receiving a 30-day PrEP supply. Follow-up visits were scheduled at week 4 after enrollment and quarterly thereafter. Main outcomes were LTPE (3+ follow-up visits within 52 weeks of enrollment) and HIV incidence. A multivariable model controlling for country, education, gender, substance use, STIs, and self-reported adherence is presented.

**Results:** From March 2018-June 2021, 9522 participants were enrolled (Brazil: 3928, Mexico: 3301, Peru: 2293), with 12348.92 person-years (PY) follow-up; follow-up time accrued for LTPE analysis affected by Covid-19 restrictions was shorter in Brazil than in Mexico and Peru. Overall, 26% were aged 18-24, 94.3% cis-MSM, 5.7% TGW, 73.2% non-white and 76.0% >secondary education; 92.8% reported condomless anal sex (CAS), 17.3% sex-work, 57.8% had >5 sex partners. Overall, 8.8% attended only the enrollment visit and 68.2% showed LTPE (Brazil:80.1%; Mexico:67.2%; Peru:45.0%). Participants aged 18-24 years (aOR 0.53[95%CI:0.46-0.62]), 10 sex partners (aOR 1.48[95%CI:1.28-1.70]), reporting receptive CAS (aOR 1.24[95%CI:1.12-1.39]), complete adherence at week-4 (aOR:3.11[95%CI:2.79-3.45]) and CAS with HIV+ partner (aOR:1.48[95%CI:1.28-1.71]) were more likely. HIV incidence was 0.84/100 PY (95% CI:0.69-1.02), higher in Peru, among TGW and 18-24 years-old participants.

**Conclusion:** Same-day PrEP is feasible and safe among cis-MSM and TGW in LA. Overall LTPE was high; COVID-19 restrictive measures may partially explain the differences across countries. Social and structural levels of HIV risk need to be addressed for full PrEP benefits realization.

**Table: Factors associated with long-term PrEP engagement[1,2]**

| | | N (%) | Bivariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | | OR (95%CI) | p-value | aOR (95%CI) | p-value |
| **Country** | Brazil | 3877 (80.53) | 1 | - | 1 | - |
| | Mexico | 2454 (67.24) | **0.50 (0.44-0.56)** | **<0.0001** | **0.50(0.42-0.59)** | **<0.0001** |
| | Peru | 1957 (45.02) | **0.20 (0.18-0.22)** | **<0.001** | **0.34(0.29-0.39)** | **<0.0001** |
| **Age (years)** | 18-24 | 2229 (58.77) | **0.46(0.40-0.52)** | **<0.0001** | **0.54(0.46-0.62)** | **<0.0001** |
| | 25-34 | 3887 (68.90) | **0.66(0.58-0.75)** | **<0.0001** | **0.67(0.59-0.77)** | **<0.0001** |
| | ≥35 | 2172 (76.66) | 1 | - | 1 | - |
| **Education** | Less than secondary | 100 (49.00) | **0.91(0.80-1.04)** | **0.06** | **0.57(0.36-0.90)** | **0.02** |
| | Some secondary | 1929 (57.18) | **0.59(0.53-0.66)** | **<0.0001** | **0.76(0.68-0.86)** | **<0.0001** |
| | More than secondary | 6259 (71.91) | 1 | - | 1 | - |
| **Gender identity** | Cisgender man | 7794 (69.52) | 1 | - | 1 | - |
| | TGW | 494 (47.57) | **0.49 (0.40-0.60)** | **<0.0001** | **0.64(0.51-0.81)** | **0.0002** |
| **N° cisgender man or/and TGW sex partners** | < 5 | 3633 (66.01) | 1 | - | 1 | - |
| | 5-10 | 2297 (68.39) | **1.12(0.99-1.26)** | **0.06** | **1.15(1.01-1.31)** | **0.03** |
| | > 10 | 2358 (71.42) | **1.20(1.07-1.36)** | **0.002** | **1.48(1.28-1.70)** | **<0.0001** |
| **Receptive CAS** | Yes | 5358 (69.65) | **1.14(1.03-1.26)** | **0.01** | **1.24(1.12-1.39)** | **<0.0001** |
| | No | 2930 (65.56) | 1 | - | 1 | - |
| **CAS with partner(s) living with HIV** | Yes | 1662(76.35) | **1.50(1.31-1.71)** | **<0.0001** | **1.48(1.28-1.71)** | **<0.0001** |
| | No | 2383(67.65) | **1.14(1.02-1.27)** | **0.02** | **1.27(1.12-1.44)** | **0.0001** |
| | I don't know | 4243(65.33) | 1 | - | 1 | - |
| **Sex work** | Yes | 1340 (56.19) | **0.66(0.58-0.75)** | **<0.0001** | **0.83(0.71-0.97)** | **0.02** |
| | No | 6948 (70.52) | 1 | - | 1 | - |
| **Complete PrEP adherence at week 4[3]** | Yes | 4538 (81.84) | **3.44 (3.10,3.81)** | **<0.0001** | **3.11(2.79-3.45)** | **<0.0001** |
| | No | 3750 (51.71) | 1 | - | 1 | - |

[1]Attending 3 or more visits within 52 weeks of enrolment. Included participants for the LTPE analysis had at least 420 days of follow-up until the censoring date (30 June 2021) n=8288.

[2]Selected factors being exhibited (this is a shorter version of the original table); [3]Report of not missing any pills in the previous 30 days. OR: Odds Ratio, aOR: adjusted OR, 95%CI: 95% Confidence Interval.

## 839 DRUG RESISTANCE AND CLUSTERING PATTERNS AMONG PREVIOUS PrEP USERS WHO SEROCONVERTED

**Angela McLaughlin**[1], Junine Toy[1], Vincent Montoya[1], Paul Sereda[1], Jason Trigg[1], Amanda Granados[1], Sakshi Khanna[1], Chanson Brumme[1], Rolando Barrios[1], Julio S. Montaner[1], Jeffrey B. Joy[1]

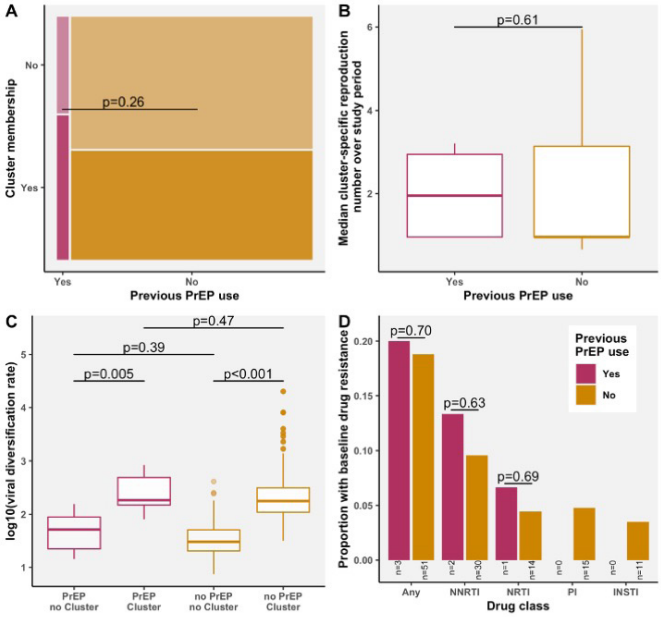
*[1]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada*

**Background:** Program evaluation is essential to public health to document success and identify areas for improvement. In British Columbia (BC), Canada, publicly funded pre-exposure prophylaxis (PrEP) has been available since January 2018 at no cost to clients, yet effects on transmission and drug resistance are uncharacterized. To evaluate the BC PrEP program we tested the hypothesis that phylogenetic clustering and drug resistance would differ between previous PrEP users who seroconverted (PUWS) compared to non-PrEP users who seroconverted (NPUWS).

**Methods:** 38539 HIV partial pol sequences generated from 10386 participants in the BC Drug Treatment Program were aligned to the HXB2 reference. WHO surveillance drug resistance mutations were extracted from the alignment. Phylogenetic trees were inferred and clusters comprising 5 or more members identified using a patristic distance cutoff of 0.02 substitutions/site, and viral diversification rates calculated for each tip. Date of first detectable viral load was used as a proxy for diagnosis date. Cluster-specific reproduction numbers were estimated using R package EpiEstim.

**Results:** From 1 January 2018 to 24 June 2021, 7465 persons had ever received PrEP via the BC program, of whom there were 15 (0.20%) PUWS between 23 October 2018 and 20 November 2020. Over this time, there were 314 NPUWS in BC. PUWS were not significantly more likely to cluster than NPUWS (chi-square: p=0.26), nor were viral diversification rates significantly higher (Kruskal test: p=0.09), or cluster-specific median reproduction numbers (Kruskal: p=0.60) (Figure 1). All unique clusters joined by PUWS were also joined by NPUWS. There were no significant differences between proportion of PUWS or NPUWS with baseline resistance to any drug class (chi-square: p=0.88, NNRTI p=0.75, or NRTI p=0.89, Figure 1d). Among 3 PUWS with baseline resistance, 2 had resistance to NNRTI, 2 to NRTI, and 0 to PI or InSTI. PUWS with the most baseline drug resistance to NRTIs had the highest proportion of days not covered by PrEP medication based on dispensing records (0.4 versus median 0.056), the longest gap with no refill (155 days versus median 22), and only 64 days lapse between last prescription and diagnosis date (median 200).

**Conclusion:** Previous PrEP use among seroconverters in BC was not associated with phylogenetic clustering, viral diversification rates, cluster-specific reproduction numbers, or baseline drug resistance. These results strongly highlight the success of the PrEP program in BC.




A comparison of the proportion of PUWS and NPUWS who joined phylogenetic clusters, using a two-sided chi-squared statistical test. B) The median cluster-specific reproduction number (of clusters with 20 or more members) in the study period of clusters joined by either PUWS or NPUWS was compared using a Kruskal-Wallis test. C) The phylogenetic viral diversification rate was compared by PrEP use and by clustering using a Kruskal-Wallis test, followed by pairwise Mann-Whitney tests. D) The proportion of PUWS and NPUWS with baseline drug resistance mutations to any or specific drug classes were compared using two-sided chi-squared tests.

## 840 A RETROSPECTIVE ANALYSIS OF BONE LOSS IN EMTRICITABINE/TENOFOVIR THERAPY FOR HIV PrEP

**Joseph C. Chang**[1], Duy Do[2], Hector M. Delgado[1], An Huynh[3]

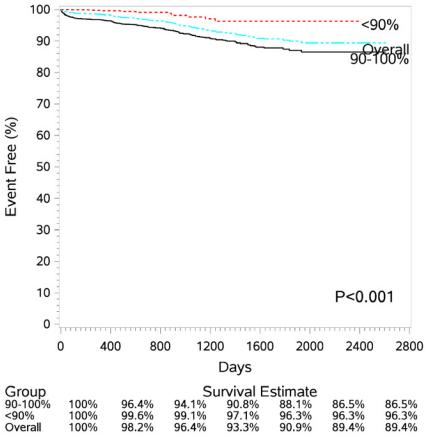
*[1]Kaiser Permanente Medical Center, Los Angeles, CA, USA, [2]Kaiser Permanente Southern California, Pasadena, CA, USA, [3]Kaiser Permanente, Los Angeles, CA, USA*

**Background:** FTC-TDF is FDA approved for the treatment of HIV infection and PrEP. It is known to cause bone loss in about 1-3% of HIV treated patients. However, a large meta-analysis on TDF in 2020 did not yield a significant bone loss result in PrEP patients. Long-term large randomized or retrospective studies address bone loss in FTC-TDF therapy for PrEP are also limited. Hence, this study aims to address the risk of osteopenia in a real life setting for patients on FTC-TDF for PrEP.

**Methods:** In this retrospective study, patients on FTC-TDF for PrEP from 2012-2020 without any prior history of bone loss in the Southern California region (N=7,698) were studied for the following criteria: bone density during follow-up, medication adherence, age, sex, race, history of HepB/HepC/DM CVD/CKD/HTN, eGFR, and BMI. Data was extracted from the Kaiser Permanente HealthConnect System. Adherence was defined using the proportion of days covered (PDC) ratio. Patients were divided into groups based on their follow-up bone density, T-score ≤ -1 (osteopenia and osteoporosis) vs. > -1 (normal). Descriptive statistics was used to compare patient characteristics between these two groups. A Cox proportion proportional hazards model was used to estimate the relationship between patient characteristics and bone loss for up to 7 years following their most recent PrEP episode.

**Results:** 3% (217/7,698) were found to have osteopenia after the start of therapy. High compliance rate, white race, Hep B, DM, CVD, CKD, HTN, and baseline eGFR<90 had a higher rate of osteopenia. Significantly higher rate of bone loss was also observed in patients with higher PDC ratio, PDC 90-100% (90.8%) vs. PDC <90% (9.2%). Kaplan-Meier curve showed event-free rate of osteopenia decreased with time (89.4% In 6.5yrs); PDC 90-100% group had greater reduction of event free rate (86.5 vs 96.3% in 6.5 yrs). Survival analysis showed statistically significant hazard ratio (HR) in patients with PDC 90-100%, Hep B, CVD, CKD, HTN, and baseline eGFR<90. However, when adjusted for all variables, the adjusted HR only showed patients with PDC 90-100% to be at significant risk for osteopenia (5.36 [3.34, 8.61]).

**Conclusion:** Our cohort showed a similar rate of osteopenia compared to HIV patients. Event-free rate is inversely proportional with time and intensity of exposure. High compliance rate and prolonged exposure may have higher risk of developing osteopenia. Hence routine check-up for osteopenia may be needed for these two groups of patients.




## 841 TRENDS IN THE PREEXPOSURE PROPHYLAXIS CONTINUUM AMONG US LATINX MSM

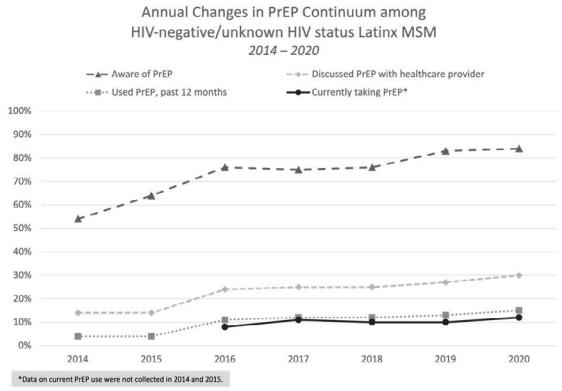
**Michael Barry**[1], David Katz[2], Roxanne P. Kerani[2], Travis Sanchez[3], Jane J. Lee[2]
*[1]Public Health–Seattle & King County, Seattle, WA, USA, [2]University of Washington, Seattle, WA, USA, [3]Emory University, Atlanta, GA, USA*

**Background:** Latinx men who have sex with men (MSM) in the U.S. have yet to experience declines in HIV diagnosis rates over the past decade. Latinx MSM report comparable or lower rates of pre-exposure prophylaxis (PrEP) use relative to their White or Black counterparts, and PrEP continuum data among Latinx MSM residing outside large metropolitan areas are limited. We describe trends in the PrEP continuum among Latinx MSM in a nationwide online sample of MSM.

**Methods:** We analyzed data from the 2014-2020 cycles of the American Men's Internet Survey, an annual online cross-sectional behavioral survey of cisgender MSM (assigned male sex at birth, age >15 years, residing in the U.S., reported oral or anal sex with another man). Our analysis included participants who were Latinx, reported HIV-negative or unknown status, and answered yes or no to a question regarding PrEP awareness. We calculated PrEP continuum outcomes by tabulating individuals at each of 4 steps of the continuum (awareness, discussed PrEP with provider, used PrEP in last year, current PrEP use) overall and by year. We used multivariate logistic regression to identify correlates of PrEP use in the past 12 months.

**Results:** From 2014-2020, 72,931 surveys were completed, of which 9011 (11%) met study inclusion criteria. Overall, 6,821 (76%) of participants reported being aware of PrEP, 2,130 (24%) reported having discussed PrEP with a healthcare provider in the past 12 months, 1,039 (12%) reported using PrEP in the past 12 months, and 773 (9%) reported currently using PrEP. All PrEP continuum outcomes rose from 2014-2020 (Figure 1), but the proportion who reported current PrEP use remained low (12%) in 2020. In multivariate analyses PrEP use was disparate across subgroups; younger Latinx MSM and those with lower levels of education had lower odds of PrEP use in the last 12 months in 2020 (aoR:0.24, 95% CI:0.17-0.34 for ages 15-19 vs. >40, aOR:0.39, 95% CI:0.24-0.64 for<="" div="">

**Conclusion:** Despite improvements across the PrEP continuum from 2014-2020, only 1 in 9 Latinx MSM reported current PrEP use in 2020. Disparities in PrEP use among Latinx MSM demonstrate that tailored strategies to address specific gaps and reduce new infections must take into account the diverse characteristics and contexts of Latinx MSM that can pose barriers to PrEP use.




## 842 A TOOL TO ASSESS HIV PREVENTION READINESS OF ADOLESCENT GIRLS AND YOUNG WOMEN

**Geetha Beauchamp**[1], Sybil Hosek[2], Deborah Donnell[1], Gary Chan[3], Bonnie Dye[4], Brian Flaherty[3], Peter Anderson[5], Nyaradzo M. Mgodi[6], Linda-Gail Bekker[7], Sinead Delany-Moretlwe[8], Connie L. Celum[3]
*[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]Stroger Hospital of Cook County, Chicago, IL, USA, [3]University of Washington, Seattle, WA, USA, [4]FHI 360, Durham, NC, USA, [5]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [6]University of Zimbabwe, Harare, Zimbabwe, [7]Desmond Tutu HIV Foundation, Cape Town, South Africa, [8]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa*

**Background:** In open-label oral pre-exposure prophylaxis (PrEP) studies among African adolescent girls and young women (AGYW), adherence was 25%-60% in the first six months. A reliable, valid, readiness tool would help identify AGYW who are motivated to take PrEP and need adherence support.

**Methods:** At enrollment into the HPTN 082 open label PrEP study, South African and Zimbabwean women ages 16-25 were administered an HIV prevention readiness measure (HPRM), which was adapted from a validated HIV treatment readiness measure for US youth living with HIV. The key components of HPRM (25 items) included medication beliefs, connection with care, PrEP disclosure, social support and housing stability using a 5-point Likert scale. Exploratory factor analysis (EFA) using polychoric correlation, scale reliability, and predictive validity were performed on the 315 participants who responded to all items. We assessed the predictive value of HPRM scores on PrEP adherence, as measured by tenofovir-diphosphate (TFV-DP) concentration in dried blood spots, as a continuous measure and dichotomized as high PrEP adherence (≥700 fmol/punch). Persistent adherence was defined as high PrEP adherence at both months 3 and 6.

**Results:** EFA yielded 23 items with three subscales: self-efficacy (16 items), PrEP disclosure (4 items) and social support (3 items). Cronbach's α was 0.92 for the overall scale, and 0.90, 0.71 and 0.80 for the three subscales. The overall scale and the three subscales were significantly predictive of PrEP adherence when DBS TFV-DP concentration was a continuous outcome measure. For each unit increase of the overall HPRM score, TFV-DP concentration increased by 122 fmol/punch (95% CI: 33.44 to 210.67 fmol/punch, p = 0.007); the highest HPRM score equated with 610 fmol/punch on average. For PrEP efficacy subscale, TFV-DP increased by 108.76 fmol/punch (95% CI: 24.09 to 193.45 fmol/punch, p = 0.012); PrEP disclosure, 71.98 fmol/punch (95% CI: 21.59 to 122.37 fmol/punch, p = 0.005); and social support, 62.57 fmol/punch (95% CI 5.63 to 119.50 fmol/punch, p = 0.031). Only PrEP disclosure was predictive of high adherence (OR 1.37, 95% CI 1.00 to1.86, p = 0.047) and persistent high adherence (OR: 1.53, 95%CI 1.04 to 2.23, p = 0.030).

**Conclusion:** PrEP demonstration project among young African women, the HPRM scale and the three subscales demonstrated good reliability. PrEP disclosure subscale exhibited modest predictive validity of high PrEP adherence. Future work will examine utility of other subscales.

## 843 PrEP DISCONTINUATION AMONG ADOLESCENTS PrEP USERS IN BRAZIL

**Diana R. Zeballos Rivas**[1], Fabiane Soares[1], Laio Magno[1], Marcos Eustorgio[1], Leila Amorim[1], Dirceu Greco[2], Alexandre Grangeiro[3], Ines Dourado[1]
*[1]Federal University of Bahia, Salvador, Brazil, [2]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [3]Universidade Federal de São Paulo, Sao Paulo, Brazil*

**Background:** PrEP discontinuation is a challenge for PrEP programs as HIV seroconversion usually occurs in these stopping periods. Several studies with adult men who have sex with men (MSM) and transgender women (TGW) have been published, but it is still scarce for adolescent MSM and TGW. Therefore, this study aims to analyze factors associated with PrEP discontinuation.
**Methods:** PrEP1519 is the first PrEP demonstration cohort study in Latin America among MSM and TGW aged 15-19 years. It takes place in 3 large Brazilian capital cities. We included individuals enrolled in PrEP from February 2019-September 2021. PrEP discontinuation was defined as no possession of PrEP pills for more than 90 days. Participants who seroconverted or possessed PrEP were right-censored. Probabilities of non-discontinuation were estimated using Kaplan Meier. The survival distributions defined by covariates were compared using log-rank and Wilcoxon tests. Cox regression models were carried out, and adjusted hazard ratios (aHR) with 95% confidence interval were estimated.
**Results:** A total of 1146 participants started PrEP, 22% were 15-17 yo. Most were MSM (91.5%), self-identified as black/brown (70.4%). Over the study period, 53.4% were persistent users and almost half discontinued PrEP (46.6%). The probability of discontinuation within the first 12 weeks was 20.1%, and the median time to PrEP discontinuation was 168 days. Multivariate analysis showed that risk of discontinuation increased 64% in TGW (aHR: 1.64; CI: 1.24 - 2.18) when compared to MSM; and increased 68% (aHR: 1.68; CI: 1.31 - 2.15) and 31% (aHR: 1.31; CI: 1.03 - 1.66) if the risk perception for HIV was low or medium, respectively, when compared with those with high-risk perception. Having an HIV-positive partner in the past 3 months was associated with a lower risk of discontinuation (aHR: 0.58; CI: 0.36 - 0.93). Socioeconomic characteristics, housing situation and other sexual behaviors were not associated with discontinuation.
**Conclusion:** Adolescents' behaviors are dynamic and fluid; therefore, we must continually adapt to their context and respect their choices. The greater social vulnerability may have increased the risk of discontinuation in TGW. PrEP discontinuation at an early stage was associated with a disconnection between risk perception and sexual behavior. It is important to emphasize the value of PrEP as an HIV prevention tool, especially for adolescents with medium and low-risk perceptions for HIV infection, and for TGW.

Table 1. Factors associates with PrEP discontinuation among adolescents in the PrEP1519 study.

| Variables | Discontinuation N/n (%) | Log-rank test p-value | Bivariate analysis HR (95%CI) | Multivariate analysis¥ aHR (95%CI) |
|---|---|---|---|---|
| Sub-population | | <0.001 | | |
| Men who have sex with men | 1049/476 (45.4) | | 1 | 1 |
| Transgender women | 97/58 (59.8) | | 1.65 (1.26 - 2.17) | 1.64 (1.24 - 2.18) |
| Risk perception for HIV | | <0.001* | | |
| Low | 351/183 (52.1) | | 1.67 (1.31 - 2.14) | 1.68 (1.31 - 2.15) |
| Medium | 502/230 (45.8) | | 1.30 (1.02 - 1.64) | 1.31 (1.03 - 1.66) |
| High | 255/98 (38.4) | | 1 | 1 |
| Having an HIV positive partner | | 0.010 | | |
| No/Do not know | 1054/497 (47.2) | | 1 | 1 |
| Yes | 58/18 (31.0) | | 0.53 (0.33 - 0.85) | 0.58 (0.36 - 0.93) |

aHR: adjusted Hazard Ratio; CI: Confidence interval.
*Wilcoxon test.
¥Proportional hazard assumption was fulfilled; evaluated using Schoenfeld residuals.

## 844 ECOLOGICAL MOMENTARY ASSESSMENT TO EXPLORE THE POTENTIAL OF ON-DEMAND PrEP FOR YMSM

**Lisa Hightow-Weidman**[1], Zachary Soberano[1], Bryce Stamp[1], Kimberly Powers[1], Sybil Hosek[2], Jacob Stocks[1], Matthew Rosso[1], Alyssa Vecchio[3], Keith J. Horvath[4]
*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Stroger Hospital of Cook County, Chicago, IL, USA, [3]University of New Mexico, Albuquerque, NM, USA, [4]San Diego State University, San Diego, CA, USA*

**Background:** Despite the availability of highly effective daily oral HIV pre-exposure prophylaxis (PrEP), uptake and adherence among young men who have sex with men (YMSM) remains low. On-demand, or event-driven, PrEP may overcome some daily PrEP barriers and is effective among adult MSM; however, it has not been examined among YMSM. Executive-function and other developmental considerations may challenge on-demand PrEP as a viable strategy for YMSM. We conducted an ecological momentary assessment (EMA) study with YMSM, using two different question types, to assess their ability to predict sex, a necessary condition for effective on-demand PrEP use.
**Methods:** Participants were recruited nationwide and completed a brief daily survey for 8 weeks to collect the following: 1) engagement in sex in the prior 24-hour period; and 2) likelihood they would have sex in the following 24-hour period with two question types: a) "gist-based" questions (response options from "not at all likely" to "very likely"); b) "verbatim" questions (continuous response options from 0-100%). On days when participants reported having sex, additional questions regarding timing of sex, partner type, condom and alcohol/drug use were asked.
**Results:** 120 youth (median age 21 years) were enrolled. A majority (53%) were men of color. Nearly half reported current (28%) or prior (15%) PrEP use. Overall study retention was 99%. Participants completed 6563 daily EMAs (98% of all potential EMA responses) and reported 845 anal sex events (952 sex acts). Of 704 anal sex events for which an EMA prediction was available the day prior, 42% (n=295) were instances in which participants had indicated in a gist-based question that they were unlikely or very unlikely to have sex in the next 24 hours. Findings with verbatim-based questions were similar, with 49% (n=342) of sex events preceded a day earlier by participants reporting that they were <50% likely to have sex the next day. Participants reported that 38%, 30% and 32% of sex events were with a main, casual or anonymous sex partner, respectively. For most anal sex events (71%), participants indicated that they knew they were going to have sex <2 hours before the episode, and 73% of anal sex acts were condomless.
**Conclusion:** The high frequency of condomless sex underscores the need for effective PrEP strategies among YMSM. Challenges in predicting sex with sufficient lead time for event-driven PrEP suggest that interventions are needed for YMSM choosing this prevention strategy.

## 845 PrEP USE PERSISTENCE AMONG KENYAN WOMEN WHO INITIATED PrEP DURING PREGNANCY

**Jillian Pintye**[1], John Kinuthia[2], Anna Larsen[1], Felix Abuna[3], Ben Ochieng[3], Nancy Ngumbau[2], Julia Dettinger[1], Laurén Gomez[1], Jessica E. Haberer[4], Grace John-Stewart[1], Jared Baeten[5]
*[1]University of Washington, Seattle, WA, USA, [2]Kenyatta National Hospital, Nairobi, Kenya, [3]University of Nairobi, Nairobi, Kenya, [4]Massachusetts General Hospital, Boston, MA, USA, [5]Gilead Sciences, Inc, Foster City, CA, USA*

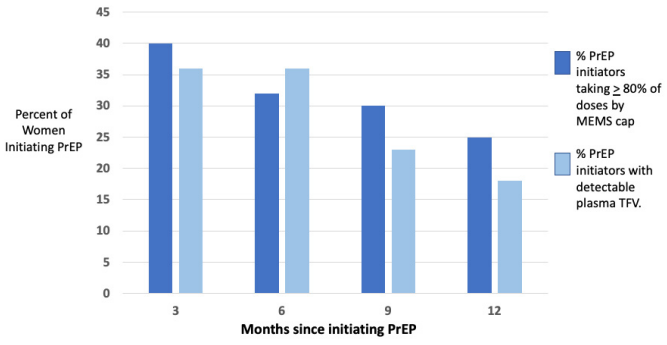
**Background:** PrEP implementation is scaling up among pregnant and breastfeeding women in East and Southern Africa, yet few data exist on longitudinal PrEP use in this population. We evaluated PrEP use persistence through postpartum among Kenyan women who initiated PrEP during pregnancy.
**Methods:** We prospectively analyzed data from a subset of participants in the PrIMA Study (NCT03070600) who enrolled during the 2nd trimester of pregnancy, initiated PrEP during pregnancy, and were followed through 9 months postpartum. PrEP persistence and self-reported adherence were assessed at each follow-up visit (monthly in pregnancy; 6 weeks, 14 weeks, 6 months, 9 months postpartum). Predictors of PrEP persistence through 9 months postpartum were identified using Poisson regression models clustered by site.
**Results:** Overall, 361 participants enrolled during the 2nd trimester, initiated PrEP during pregnancy, and met inclusion criteria for this analysis (50% of all PrEP initiators in PrIMA). Among the subset, the median gestational age at PrEP initiation was 30 weeks (IQR 25-33), 91% of participants were married, and 20% had a partner known to be living with HIV. At 9-months postpartum, 58% had persisted with PrEP use since initiation during pregnancy and among those 53% reported not missing any PrEP pills in the last 30 days. Participants with partners known to be living with HIV were 1.5 times more likely to persist with PrEP use at 9-months postpartum compared to participants with partners who were HIV-negative or of unknown HIV status (Risk Ratio[RR]=1.53, 95% CI:1.32-1.77, p<0.001). Compared to participants <24 years, those ≥24 years were 1.6 times more likely to persist with PrEP use at 9-months postpartum (RR=1.59, 95% CI:1.28-1.98, p<0.001). PrEP persistence at 9-months postpartum was also associated with testing positive for syphilis in pregnancy and having a prior pregnancy (p<0.05). There was no association between PrEP persistence and depression or intimate partner violence. Among those <24 years, lower educational attainment and higher number of lifetime sexual partners were also associated with PrEP persistence (p<0.05).
**Conclusion:** In this prospective analysis among women who initiated PrEP during pregnancy, PrEP persistence through postpartum was common and associated with having risk factors for HIV acquisition and older age, with moderate levels of self-reported adherence. Adherence interventions should prioritize younger pregnant women and those that may not know their partner's HIV status.

## 846 ORAL PrEP USE AMONG SOUTH AFRICAN WOMEN WITH PLANS FOR PREGNANCY

**Lynn T. Matthews**[1], Manjeetha Jaggernath[2], Yolandie Kriel[2], Christina Psaros[3], Patricia M. Smith[1], Kara Bennett[4], David R. Bangsberg[5], Craig W. Hendrix[6], Norma Ware[7], Jared Baeten[8], Kathleen E. Hurwitz[9], Jessica E. Haberer[3], Jennifer Smit[10]
*[1]University of Alabama at Birmingham, Birmingham, AL, USA, [2]MatCH, Durban, South Africa, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Bennett Statistical Consulting, Inc, New York, NY, USA, [5]Oregon Health and Sciences University, Portland, OR, USA, [6]The Johns Hopkins Hospital, Baltimore, MD, USA, [7]Harvard Medical School, Boston, MA, USA, [8]University of Washington, Seattle, WA, USA, [9]Social and Scientific Systems, Inc, Durham, NC, USA, [10]MatCH Research Unit, Durban, South Africa*

**Background:** Women exposed to HIV need strategies to mitigate periconception HIV acquisition. We evaluated longitudinal use of TDF/FTC as PrEP among HIV-uninfected women with personal or partner plans for pregnancy in Durban, South Africa.
**Methods:** We enrolled HIV-uninfected women, aged 18-35 years, reporting personal or partner plans for pregnancy, and a partner with HIV or of unknown-serostatus. Safer conception counseling including TDF/FTC as PrEP was offered at quarterly visits. PrEP was supplied with an electronic pill cap and quarterly adherence counseling. We followed women for at least 1 year. We defined adherence as the number of pill cap openings divided by number of days of expected PrEP use. Plasma tenofovir was measured quarterly (detectable defined as >0.31ng/mL) from PrEP initiators.
**Results:** Between November 2017 and January 2020 we enrolled 330 women with median age 24 (IQR: 22-27) years. Partner HIV-serostatus was unknown by 316 (96%). Among 327 women completing safer conception counseling, 195 (60%) initiated PrEP. Among PrEP initiators, overall median (IQR) adherence during periconception follow-up was 63% (42%-83%). Adherence was highest during the first 3 months (73%) and declined over time (62%, 55%, and 62% at 6, 9, and 12 months, respectively). The proportion of women taking at least 80% of PrEP was 40%, 32%, 30%, and 25% at 3, 6, 9, and 12 months. Similarly, tenofovir was detected in 36%, 31%, 23%, and 18% of PrEP initiators at 3, 6, 9, and 12 months. Eleven HIV-seroconversions were observed among 315 participants contributing 272 person-years of follow-up for an IR 4.04 per 100 person-years (95%CI: 2.24-7.30). Among women who never accessed PrEP, there were five seroconversions among 122 participants contributing 108 person-years (IR per 100 person-years: 4.62, 95% CI: 1.92-11.1). Six seroconversions were observed among 193 PrEP initiators contributing 164 person-years (IR per 100 person-years: 3.66 95% CI: 1.64-8.15); none had detectable plasma tenofovir at seroconversion.
**Conclusion:** We observed high HIV incidence among women with personal or partner plans for pregnancy in an HIV-endemic area. We describe high periconception PrEP uptake among South African women whose partner's HIV-serostatus is unknown. Longitudinal adherence data suggest a quarter of women are able to consistently take PrEP with adherence support. Additional PrEP support strategies are needed to reduce HIV incidence among young women who choose to take periconception PrEP.

Figure 1. Twelve month adherence to periconception PrEP among Women in South Africa

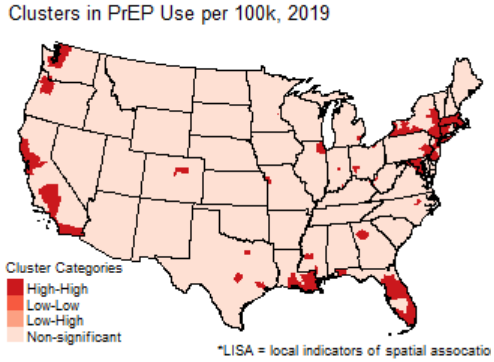



## 847 GEOGRAPHIC CLUSTERING AND PROGRESS IN PrEP USE AMONG WOMEN IN THE US: 2012-2019

New Investigator Scholar

**Brady W. Bennett**[1], Sanjana Pampati[1], Marisol Valenzuela-Lara[1], Patrick S. Sullivan[1], Jodie L. Guest[1]
*[1]Emory University, Atlanta, GA, USA*

**Background:** In 2019, Ending the HIV Epidemic (EHE) was launched to focus local, state, and federal authorities on decreasing new HIV infections in the United States by 75% in 2025 and 90% in 2030. A key tenet of this initiative is to increase utilization of preventative measures, particularly Pre-Exposure Prophylaxis (PrEP). Although PrEP uptake has risen significantly since its approval in 2012, numerous sociodemographic and area-level disparities persist. In 2019, women accounted for 18% of new HIV infections in the U.S. but only 7.4% of PrEP users.
**Methods:** This study considers the spatial distribution and clustering of PrEP uptake among women in the U.S., and calculates the estimated annual percent change (EAPC) for PrEP use in women by geographic region and state from 2012-2019. PrEP utilization/100,000 women at region, state, and county-levels were accessed through AIDSVu.org. We utilized global and local Moran's I statistics to determine global spatial autocorrelation and to identify clusters of counties where the PrEP utilization/100,000 were either significantly higher or lower than average rates in both the index and surrounding counties. Clusters were plotted in a local indicators of spatial association (LISA) map.
**Results:** County-level spatial clustering of PrEP utilization, measured by categorization of significant local spatial autocorrelation, was primarily found in major metropolitan areas in California, Florida, southern Louisiana, the Atlanta, GA metroplex, the Northwest, and along the eastern seaboard from Washington D.C. to Boston, MA with smaller clusters in Chicago, IL and Denver, CO. In our analysis of EAPC, the largest region-specific change for PrEP utilization was in the Midwest (13.3%) and the smallest in the Northeast (3.8%), while the largest increase in EAPC by state was seen in Louisiana (31.2%) and the largest decrease was seen in Massachusetts (-10.4%).
**Conclusion:** Achieving an end to the HIV epidemic requires increased utilization of PrEP along with other key prevention measures among women at risk. There is significant clustering of PrEP uptake in major metropolitan areas, particularly those in the EHE focus counties, confirming progress. However, while uptake has increased in many areas, there are geographic and temporal disparities. Understanding where PrEP uptake is increasing (and not) relative to surrounding areas as well as improved education about PrEP is needed to change the HIV epidemic among women in the United States and globally.




## 848 EXTENDED-RELEASE NALTREXONE LOWERS INJECTION USE IN JUSTICE-INVOLVED PERSONS WITH HIV

**Audun J. Lier**[1], Nikhil Seval[1], Brent Vander Wyk[1], Angela Di Paola[1], Sandra Springer[1]
*[1]Yale University, New Haven, CT, USA*

**Background:** Opioid use disorder (OUD) and injection drug use (IDU) behavior are both highly prevalent among justice involved individuals, with the latter increasing risk for HIV acquisition. Medications for opioid use disorder (MOUD), including extended-release naltrexone (XR-NTX), are associated with increased retention on antiretroviral therapy (ART) and viral suppression in persons with HIV (PWH). However, the effect of XR-NTX on IDU risk behavior is incompletely studied. This relationship was examined in justice involved individuals with HIV and OUD. We hypothesized that XR-NTX would reduce IDU risk behavior following release from prison or jail.
**Methods:** A secondary analysis was performed of data obtained from a NIDA-funded double-blind placebo controlled randomized trial of persons in prison and jail with HIV and OUD who were randomized 2:1 to receive either monthly XR-NTX or placebo prior to release with 5 more subsequent injections in the community post-release. Participants were assessed monthly and data was

collected on self-reported daily IDU pre-incarceration as well as monthly post-incarceration for 6 months via the timeline follow back technique. Time to first opioid injection and number of consecutive days abstinent from injection were analyzed. Mean proportion of monthly opioid use was calculated and a time to event analysis was performed.
**Results:** A total of 88 individuals were included for this analysis with 62 receiving XR-NTX and 26 placebo. The mean age of participants was 45.7 years and both groups were predominately male, black, and Hispanic. Seventy four (84.1%) were prescribed ART, 51 (57.9%) had an HIV RNA < 200 copies/mL at baseline and 62 (70.5%) were HCV antibody positive. There was no difference in IDU risk behaviors in the intention to treat analysis, however the as treated analysis for those who received 3 or more injections of XR-NTX had significantly lower mean proportion of IDU days by month 5 of follow-up (0.04 vs 0.26, p<0.05) and had a longer time to IDU relapse (Mean=136.4 vs 53.2 days, p=0.002) versus placebo. There was no difference after month 6 of follow-up when the parent study intervention ceased.
**Conclusion:** In this cohort of justice involved PWH and OUD, XR-NTX was associated with reduced IDU risk behavior and a longer time to IDU relapse. Our results suggest that integration of MOUD with HIV treatment can reduce IDU risk behavior. Further public health efforts are warranted to promote harm reduction via uptake and maintenance of MOUD in PWH with OUD.

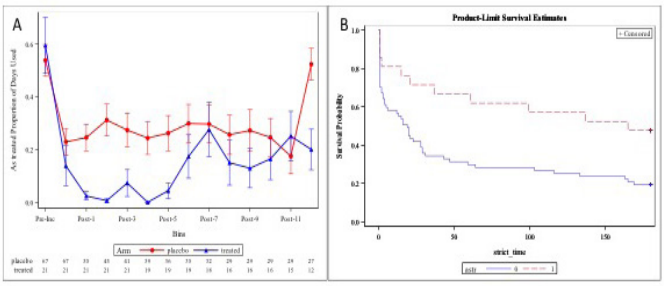


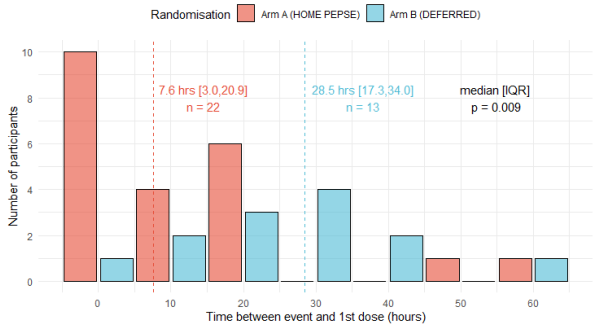

Figure 1. A) As treated bin analysis of mean proportion of IDU by month of follow-up, where treatment group refers to those who received three or more injections of XR-NTX. B) As treated time to event (IDU) analysis (Kaplan Meier).

## 849 SELF-START HOME PEPSE TO REDUCE UPTAKE TIME AND INCREASE PEPSE EFFICACY: RCT

**Epidemiology/Public Health:**

**Julie Fox**[1], Julianne Lwanga[2], Achyuta Nori[2], Amanda Clarke[3], Ming J. Lee[4], Orla McQuillan[5], Lesedi M. Ledwaba-Chapman[1], suna mantori[3], Cassie Fairhead[2], fiona ryan[2], Yanzhong M. Wang[6], anatole menon-johansson[2]
*[1]King's College London, London, UK, [2]Guy's and St Thomas' NHS Foundation Trust, London, UK, [3]Brighton and Sussex University Hospitals NHS Trust, Brighton, UK, [4]Imperial College London, London, UK, [5]Manchester Royal Infirmary, manchester, UK, [6]King's College Hospital, London, UK*

**Background:** Effectiveness of Post exposure prophylaxis (PEPSE) correlates with speed of uptake following HIV exposure. Time taken travelling to and obtaining PEPSE at sexual health/ emergency units can reduce efficacy and prevent people accessing PEPSE. We hypothesized that advanced provision of a 5-day PEP starter pack (HOME PEPSE) for men who have sex with men (MSM) to keep at home and self- initiate if required, would reduce time to first dose following HIV exposure, but not impact HIV risk behavior.
**Methods:** Phase IV, randomised, prospective, open label, study. MSM at medium risk of acquiring HIV were randomized (1:1) to immediate (ARM A) or deferred (ARM B) Home PEPSE. Duration of study was 48 weeks (Arm A) and 72 weeks for (Arm B) who accessed PEPSE through standard of care from week 0-48 and received HOME PEPSE week 48-72. Every 12weeks, participants self-completed mental health/ risk behaviour surveys and had HIV/STI testing. HOME PEPSE comprised a 5-day pack of FTC-TDF/Maraviroc taken following potential exposure to HIV. Upon uptake, participants completed a risk questionnaire; PEPSE continuation was physician directed. Appropriate uses of PEP were included in primary analysis. Time to first dose between treatment arms was compared using a two-sided Mann-Whitney U test.
**Results:** 139 participants were randomised: 69 (ARM A) and 70 (ARM B). Median age 30years [IQR: 26-39], 75% white, 55% UK born and 72% university educated. 33 in ARM A and 15 in ARM B were eligible for primary analysis. Median time from exposure to first dose was 7.6 hours [3.0,20.9] for ARM A and 28.5 hours [17.3,34.0] for ARM B (p < 0.01). The most reported reason for PEPSE uptake was receptive anal sex with a man of unknown HIV status (81% cases). Uptake of HOME PEPSE was appropriate in 29/ 33 cases (88%, 95% CI: 73-95%). ARM B had almost double the number (same median and IQR) of missed opportunities for PEPSE uptake than ARM A (268 versus 474 :p=0.625): 9/12 (75%) participants reporting >10 missed opportunities for PEP were in ARM B. No change in number of condomless anal sex acts in previous 3 months from week 0 to 48 in Arm A or arm B (512 versus 911: p = 0.215). One person in Arm B acquired HIV. HOME PEPSE was well tolerated.
**Conclusion:** HOME PEPSE was taken appropriately by MSM, and dramatically reduced time from exposure to first dose, with no impact on safety. Furthermore, HOME PEP may reduce number of missed opportunities for PEPSE. This approach may be incorporated into HIV prevention guidelines.




## 850 IMPLEMENTATION OF A POST-EXPOSURE PROPHYLAXIS HOTLINE IN WASHINGTON, DC

**Megan Coleman**[1], Jason Beverley[2], Annika Bergstrom[3], Kate Drezner[1], Rachel Harold[1], Michael Kharfen[1], Amanda B. Spence[4], Camilla Stanley[1], Ashlee Wimberly[1], Adam Visconti[4]
*[1]DC Department of Health, Washington, DC, USA, [2]AIDS Treatment Activists Coalition, Washington, DC, USA, [3]George Washington University, Washington, DC, USA, [4]Georgetown University, Washington, DC, USA*

**Background:** Non-occupational post exposure prophylaxis (nPEP) is an effective HIV prevention strategy, yet implementation has been limited. To address this gap, the DC Department of Health launched a 24/7 clinician staffed nPEP telephone hotline paired with 5-7 day starter nPEP regimens through local contract pharmacies and follow up at a government run sexual health clinic. Callers who met nPEP CDC criteria, were located in DC, and were able to pick up a starter prescription or initiate nPEP at the clinic within 72 hours were eligible.
**Methods:** Four staff and two community trainings were conducted prior to project launch. Four strategically located contract pharmacies dispensed nPEP bridge prescriptions and were tested with secret shoppers prior to launch. A city-wide nPEP social media and advertising campaign was consecutively launched with the hotline. Modifications to planned implementation were tracked and communicated to partners consistently to ensure fidelity. Caller demographic data was collected and clinical data abstracted from the electronic medical record. Reach, Evaluation, Adoption, Implementation, and Maintenance (RE-AIM) framework was used to evaluate the implementation of the nPEP Hotline at 6 months.
**Results:** Between 4/1/2021 and 9/16/2021 there were 338 callers; 59% (n=201/338) were eligible for nPEP and referred for nPEP initiation; 84% (n=173/201) attended an initial nPEP clinic consultation; 55% (n=95/201) attended a 28-day follow-up. Sixty-eight percent of those that followed-up at 28 days (n=65/95) transitioned to pre-exposure prophylaxis (PrEP). Seventy percent (n=141/201) of eligible callers received a bridge prescription and 30% (n=60) received same day nPEP at their intake visit. Forty-five percent (n=91/201) of referred individuals were located in ZIP codes representing DC's top ten HIV incidence rates. Compared to individuals diagnosed with HIV in 2019, the nPEP cohort was more likely to be White than Latino/a/x (OR: 0.38 95% CI 0.19-0.75) or Black (OR: 0.12, 95% CI 0.064-0.21) with a larger proportion of White MSM (25.2%) than 2019 new diagnosis (7.3%), p<.001
**Conclusion:** The nPEP provider hotline was successfully launched and 6-month metrics indicate uptake among some priority populations in DC. However, uptake among the populations most impacted by HIV was not fully recognized. Current and future efforts will focus on increased awareness and uptake in priority populations, retention in care, and transitions to PrEP where indicated.

## 851 RCT OF iTAB PLUS MOTIVATIONAL INTERVIEWING FOR PrEP ADHERENCE IN TRANSGENDER PERSONS

**Sheldon Morris**[1], Sonia Jain[1], Jill Blumenthal[1], Robert Bolan[2], Michael Dubé[3], Philip Henderson[4], Katya Corado[5], Feng He[1], Leah Burke[1], Peter Anderson[6], David J. Moore[1]

*[1]University of California San Diego, La Jolla, CA, USA, [2]Los Angeles LGBT Center, Los Angeles, CA, USA, [3]University of Southern California, Los Angeles, CA, USA, [4]Family Health Centers of San Diego, San Diego, CA, USA, [5]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA, [6]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** Transgender individuals are at high risk for HIV, with transgender women having some of the highest incident rates. Use of preexposure prophylaxis (PrEP) among transgender persons at risk for HIV are dependent on adherence and may require enhanced interventions customized for transgender individuals.

**Methods:** This study was a parallel two arm 1:1 randomized controlled trial of a tailored texting intervention for PrEP adherence in transgender individuals, individualized Texting for Adherence Building (iTAB), with and without brief motivational interviewing (bMI) via telephone for 3 sequential days of not reporting dose taking by text over 48 weeks of follow up. The primary endpoint was a binary composite outcome derived from dried blood spot (DBS) tenofovir (TFV-DP) concentrations at both week 12 and week 48 (or the last on-drug visit) of ≥1246 fmol/punch consistent with ≥7 doses per week (i.e., near perfect adherence). Secondary outcomes included i) DBS TFV-DP concentrations of ≥719 fmol/punch consistent with 4 doses per week (i.e., adequate adherence) and ii) the mean self-reported adherence by daily text message response.

**Results:** Between June 2017 and September 2020, 255 transgender individuals were randomized to iTAB or iTAB+bMI. Adherence for the primary outcome for > 1246 fmol/punch was 49.1% for 57 transgender men, 37.3% for 19 nonbinary individuals and 31.0% for 145 transgender women. Adherence for the secondary outcome for > 719 fmol/punch was 57.9% for transgender men, 47.1% for nonbinary individuals and 44.1% for transgender women. Including all gender identities adherence was not statistically different between iTAB+bMI to iTAB alone but there was a statistically significant difference in self-reported adherence. Those in the iTAB-bMI arm reported taking their daily dose a mean of 59.8% of days versus 48.7% of those in the iTAB alone arm (p=0.011). Stratification by gender category revealed this effect was primarily due to an increase in self-reported adherence in transgender women where the mean percent of daily reported dose taking was 60.1% in the iTAB-bMI arm compared to 40.8% in the iTAB alone arm (p=0.002). Among transgender women there was adequate adherence (> 719 fmol/punch) in 39/75 (52%) in the iTAB+bMI arm compared to 25/70 (35.7%) in the iTAB alone arm (p=0.065).

**Conclusion:** Using an automated adherence reminder (iTAB) with a telephone delivered motivational interviewing intervention could increase adequate adherence to FTC/TDF for PrEP among transgender women

| Self-reported Adherence Outcomes in the iM-PrEPT Study | | | |
|---|---|---|---|
| | iTAB | iTAB+bMI | |
| | N (%) | N (%) | *p* value |
| ≥ 1246 fmol/punch at week 12 and the last DBS visit at week 24, 36, or 48 (near perfect adherence) | | | |
| Entire cohort (N=255,N1=127,N2=128) | 44 (34.7) | 49 (38.3) | 0.603 |
| Transgender men (N=57,N1=27,N2=30) | 14 (51.9) | 14 (46.7) | 0.793 |
| Transgender women(N=145,N1=70,N2=75) | 18 (25.7) | 27 (36.0) | 0.211 |
| Non-binary (N=51,N1=28,N2=23) | 11 (39.3) | 8 (34.8) | 0.779 |
| ≥ 719 fmol/punch at week 12 and the last DBS visit at week 24, 36, or 48 (adequate adherence) | | | |
| Entire Cohort (N=255,N1=127,N2=128) | 55 (43.3) | 67 (52.3) | 0.169 |
| Transgender men (N=57,N1=27,N2=30) | 16 (59.3) | 17 (56.7) | >0.999 |
| Transgender women(N=145,N1=70,N2=75) | 25 (35.7) | 39 (52.0) | 0.065 |
| Non-binary (N=51,N1=28,N2=23) | 13 (46.4) | 11 (47.8) | >0.999 |
| Mean (SD) percentage of 'Yes' responses received out of text received | | | |
| Entire Cohort (N=241, N1=118, N2=123) | 48.7 (32.7) | 59.8 (31.0) | 0.011 |
| Transgender men(N=55, N1=26, N2=29) | 62.0 (29.1) | 62.8 (32.6) | 0.723 |
| Transgender women(N=136,N1=63,N2=73) | 40.8 (33.6) | 60.1 (30.9) | 0.002 |
| Non-binary(N=48, N1=27, N2=21) | 53.5 (30.7) | 54.5 (29.9) | 0.934 |

N: overall sample size; N1: iTAB sample size; N2: iTAB+bMI sample size

## 852 HIV TESTING AND PrEP AMONG U.S. TRANSGENDER WOMEN AND MEN, 2012–2019

**Karen W. Hoover**[1], Ya-Lin A. Huang[1], Weiming Zhu[1], Anne A. Kimball[1], Evelyn J. Olansky[2], Asa Radix[3]

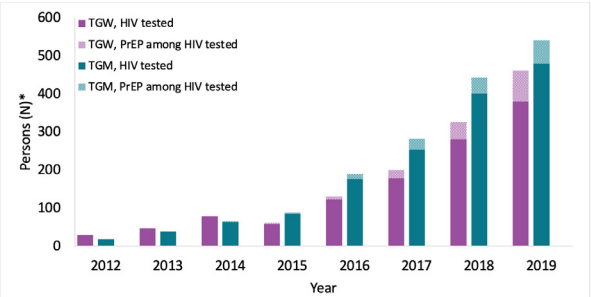
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]Social and Scientific Systems, Inc., DLH Holdings, Atlanta, GA, USA, [3]Callen-Lorde Community Health Center, New York, NY, USA*

**Background:** Transgender persons (TGP), especially transgender women (TGW), have a high lifetime risk of acquiring HIV. More than 90% of TGW either use or want to use gender-affirming hormone therapy (GAHT), but preexposure prophylaxis (PrEP) use among TGW has been low. Healthcare encounters for GAHT can provide opportunities for HIV testing and PrEP initiation. Our objective was to estimate the provision of HIV prevention services among TGP who have been prescribed GAHT.

**Methods:** We analyzed data in the 2012-2019 MarketScan database that can be weighted for nationally representative information on diagnoses, procedures, and prescriptions for health services provided to persons with commercial health insurance. We estimated the number of persons aged ≥18 years with ICD-9/10 codes for gender identity disorder/gender dysphoria from 2012–2019. We defined a TGW as a person with a relevant code and who was prescribed feminizing GAHT, and a transgender man (TGM) as a person with a code and prescribed masculinizing GAHT. To estimate the prevalence of HIV tests and PrEP prescriptions, we excluded persons with HIV diagnoses and restricted the sample to persons continuously enrolled in their health plan ≥6 months each year. We used procedural codes to identify HIV tests PrEP prescriptions. We estimated the annual prevalence of HIV testing, and PrEP prescriptions among those tested.

**Results:** The weighted number of persons with TG-related codes increased from 7,993 (6.7 per 100,000 enrolled persons) in 2012 to 94,168 (75.6 per 100,000) in 2019 (Ptrend <.0001). The weighted number of TGP prescribed GAHT also increased from 1,961 (24.5%) in 2012 to 38,110 (40.5%) in 2019. HIV testing and PrEP prescriptions increased among both TGW and TGM (Figure). In 2012, 9.9% of TGW were tested for HIV and none of those tested were prescribed PrEP; in 2019, 22.5% of TGW were tested and 17.6% were prescribed PrEP. In 2012, 6.6% of TGM were tested for HIV and none of those tested were prescribed PrEP; in 2019, 17.8% of TGM were tested and 11.5% were prescribed PrEP. In comparison, in 2019, 5.6% of all HIV-uninfected persons were tested for HIV and 2.8% of those tested were prescribed PrEP.

**Conclusion:** HIV testing and PrEP prescriptions for TGW and TGM who were using GAHT increased over the study period, but many HIV prevention opportunities were likely missed at clinical encounters for GAHT. The health and wellbeing of TGP can be increased with holistic service models that include HIV prevention in addition to GAHT.




*Unweighted number of persons with no prior HIV diagnoses and who were continuously enrolled in their health plan ≥6 months.

Figure. HIV testing and PrEP prescriptions among transgender women (TGW) and transgender men (TGM) ≥18 years in the United States, 2012–2019

## 853 PrEP NEED AND SERVICES FOR TRANSGENDER PERSONS IN THE THRIVE PROJECT, 2015–2020

**Maria Zlotorzynska**[1], Weiming Zhu[2], Ya-Lin A. Huang[2], Kashif Iqbal[2], Mary Tanner[2], Karen W. Hoover[2]

*[1]Social & Scientific Systems, Silver Spring, MD, USA, [2]Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** Transgender persons (TGP), especially transgender women (TGW) in racial/ethnic minority populations, are at increased risk of HIV acquisition yet might face barriers to HIV prevention with preexposure prophylaxis (PrEP) such as lack of access, stigma, and medical mistrust. The objective of our study was to evaluate PrEP services received by TGW and transgender men (TGM) in the THRIVE demonstration project.

**Methods:** THRIVE supported 7 health departments to lead collaboratives comprised of community-based organizations and clinics for comprehensive HIV prevention and care. THRIVE supported activities to increase access to and use of PrEP by TGP, including outreach to TGP and navigation to PrEP services. We analyzed longitudinal data on PrEP services provided to TG THRIVE clients

from 2015 through 2020. Among HIV-negative TGW and TGM, we estimated the proportion screened and eligible for PrEP and the proportion of those eligible who were referred to PrEP services, linked to PrEP services, and prescribed PrEP.
**Results:** THRIVE enrolled 657 Black/African American (Black) and 380 Hispanic/Latino (Hispanic) TGW, and 271 Black and 105 Hispanic TGM. Proportions of HIV-negative TGW who were screened and found eligible for PrEP were similar for all racial/ethnic groups with 83.4% (448/537) of Black TGW, 83.3% (179/215) of Hispanic TGW, and 73.4% (58/79) of white TGW eligible for PrEP. Proportions of HIV-negative TGM who were screened and found eligible for PrEP were similar for all racial/ethnic groups with 63.7% (107/168) of black TGM, 67.3% (33/49) of Hispanic TGM, and 62.8% (27/43) of white TGM eligible for PrEP. Most PrEP-eligible TGW and TGM were referred to PrEP services (Figure). Among 448 Black TGW eligible for PrEP, 196 (43.8%) were linked to PrEP and 167 (37.3%) were prescribed PrEP; among 179 eligible Hispanic TGW, 126 (70.4%) were linked to PrEP and 98 (54.7%) were prescribed PrEP (Figure). Among 107 eligible Black TGM, 32 (29.9%) were linked to PrEP and 21 (19.6%) were prescribed PrEP; among 33 eligible Hispanic TGM, 18 (54.5%) were linked to PrEP and 11 (33.3%) were prescribed PrEP (Figure).
**Conclusion:** THRIVE successfully both engaged PrEP-eligible Black and Hispanic TGW and TGM for PrEP services and increased their access to PrEP. However, a large proportion of TGW and TGM referred to PrEP care were not linked or prescribed PrEP. Barriers in addition to PrEP access must be addressed to decrease these gaps.

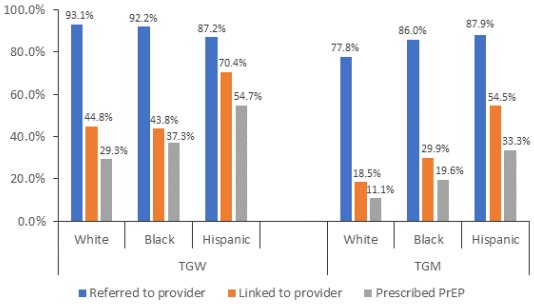



**Figure.** Referral, linkage, and prescriptions for PrEP among transgender women (TGW) and transgender men (TGM) eligible for PrEP by race/ethnicity, THRIVE demonstration project, 2015–2020

## 854 EFFECT OF ANTIMICROBIALS ON PENILE BACTERIAL DENSITY AND FORESKIN INFLAMMATION

**Tony Pham**[1], Ronald M. Galiwango[2], Daniel Park[1], Juan Enrique Salazar[1], Brenda Okech[3], Victoria M. Biribawa[3], Juliet Mpendo[3], Moses Muwanga[3], Aaron Tobian[4], Jessica Prodger[5], Rupert Kaul[2], Cindy Liu[1]
*[1]George Washington University, Washington, DC, USA, [2]University of Toronto, Toronto, Canada, [3]International AIDS Vaccine Initiative, New York, NY, USA, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]Western University, London, Canada*

**Background:** The composition of the penile microbiome, particularly abundance of specific anaerobic taxa, has been associated with HIV acquisition, potentially through promoting foreskin production of cytokines that recruit HIV target cells to the foreskin. However, little is known regarding the impact of topical or oral medications on penile microbiome composition or foreskin immunology.
**Methods:** We conducted a randomized trial with 125 HIV-negative uncircumcised men in Rakai, Uganda. Participants were randomized into five study arms (n= 25 each); the control group underwent circumcision immediately, while four intervention groups deferred circumcision for 4 weeks and received either oral tinidazole for 2 days, or one of the following topical treatments: metronidazole, clindamycin or hydrogen peroxide applied twice daily for one week then twice weekly until circumcision. We collected sub-preputial swabs at enrollment and at weeks 1 and 4 to examine the impact of treatment on total penile bacterial density using pan-bacterial 16S qPCR and examined the correlations between sub-preputial bacterial density to IL-8 and soluble E-cadherin, indicators of inflammation and impaired epithelial integrity, respectively.
**Results:** At week 1, clindamycin treatment induced the largest decrease in bacterial density (median log response ratio - MLRR= -0.79 IQR= -1.69, -0.48) and tinidazole induced the smallest decrease (MLRR= -0.26, IQR= -0.59, 0.13); intermediate effects were seen with metronidazole (MLLR= -0.68, IQR= -1.56, -0.04) and hydrogen peroxide (MLLR= -0.59, IQR= -1.19, -0.10). At week 4, all arms showed a rebound in bacterial density from week 1. Clindamycin showed the largest sustained bacterial density decrease at week 4, and tinidazole the smallest. Even though bacterial density did not correlate with immune parameters at enrollment across arms, at week 1, bacterial density correlated significantly and positively to IL-8 with metronidazole and to both IL-8 and soluble E-cadherin with hydrogen peroxide (Table 1). At week 4, only clindamycin arm showed positive correlations between bacterial density to both immune outcomes (Table 1).
**Conclusion:** Topical antimicrobial treatment and hydrogen peroxide produced significant, albeit temporary decreases in total bacterial density. Over the course of treatment, clindamycin and metronidazole enhanced the association between penile bacterial density to inflammation and decreased epithelial integrity. Future work should describe microbiome changes in greater detail.

| Study Arm | IL-8 Enrollment | IL-8 Week 1 | IL-8 Week 4 | E-cadherin Enrollment | E-cadherin Week 1 | E-cadherin Week 4 |
|---|---|---|---|---|---|---|
| Clindamycin | 0.22 | 0.40 | **0.47*** | 0.00 | -0.08 | **0.65*** |
| Metronidazole | 0.14 | **0.44*** | 0.43 | 0.04 | 0.39 | 0.43 |
| Hydrogen Peroxide | -0.25 | **0.40*** | 0.14 | 0.04 | **0.60*** | -0.04 |
| Tinidazole | -0.02 | -0.19 | -0.02 | 0.08 | -0.08 | 0.37 |

Table 1. Spearmen Correlation between bacterial density, IL-8, and E-cadherin. *P-value < 0.05.

## 855 IN SITU FORMING IMPLANTS WITH CABOTEGRAVIR FOR ULTRA-LONG-ACTING PrEP

**Ivana Massud**[1], Martina Kovarova[2], Andres Wong-Sam[1], Chuong Dinh[1], Eric Edwards[1], Victoria Mrotz[1], James Mitchell[1], Walid Heneine[1], Isabella Young[2], Roopali Shrivastava[2], J. Victor Garcia-Martinez[2], Charles Dobard[1], Gerardo Garcia-Lerma[1], Rahima Benhabbour[2]
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

**Background:** Bi-monthly Cabotegravir long-acting (CAB LA) is expected to soon be available as a new option for HIV prevention. Biodegradable in situ forming implants (ISFI) releasing CAB represent an attractive ultra-long-acting delivery platform that can provide sustained drug release for several months to years but can be removed to terminate treatment if needed. We evaluated drug release, drug tail after removal, and PrEP efficacy of CAB ISFIs in macaques
**Methods:** Two 1-ml injections of CAB ISFI (450 mg/mL CAB) were administered in the back to 6 rhesus macaques. CAB concentrations in plasma were monitored weekly for up to 6 months and in tissues every 4 weeks for up to 3 months. Implants were retrieved at week 12 in two animals to assess drug tail after implant removal. Efficacy of CAB ISFIs against rectal SHIV infection was evaluated in 4 macaques using a repeat exposure SHIV transmission model. Macaques were challenged with SHIV162p3 twice a week between weeks 4 thru 8 (n=2 macaques) or weeks 12 thru 16 (n=2 macaques) to assess durability of PrEP efficacy. Two untreated macaques were used as controls. ISFI injection sites (n=2 per animal) were monitored weekly for presence of local skin reactions including edema and erythema
**Results:** Median (range) plasma CAB levels at weeks 4 and 8 were 982 (406-1,977) and 1,950 (578-5,628) ng/mL, respectively, or about 1.5-3.5-fold higher than the benchmark concentration of 664 ng/ml (4xPA-$IC_{90}$). Implant removal in 2 macaques at week 12 resulted in a rapid decline in plasma CAB levels from a mean of 2,128 to 179 ng/ml within 3 days. In the remaining animals, median plasma CAB concentrations between weeks 12-24 were 2,136 (971-2,553) ng/mL and remained ~1.9-fold above the 4x PA-$IC_{90}$ 6 months post implantation. CAB concentrations in vaginal and rectal tissues ranged between 293-849 and 333-1,004 ng/g of tissue, respectively (Table 1). In contrast to the 2 untreated animals that were infected after one SHIV challenge, none of the 4 treated macaques were infected after a total of 32 SHIV exposures. No skin reactions were observed at the implant sites in any of the animals
**Conclusion:** CAB ISFIs implants provided sustained release of CAB above established PrEP benchmarks for up to 6 months and conferred durable protection against SHIV infection in macaques. Implants were safe and resulted in a short drug tail upon removal. Our study describes a novel biodegradable and removable CAB formulation for long-acting PrEP and supports clinical advancement in humans

| | Week 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 |
|---|---|---|---|---|---|---|---|
| Plasma ng/mL | 338 (216-464) | 982 (406-1,977) | 1,950 (578-5,628) | 2,270 (1,430-2,553) | 2,003 (1,923-2,083) | 2,528 (2,828-2,227) | 1,278 (971-1,585) |
| Vaginal tissue (ng/g) | | 293 (BLOQ-356) | 849 (238-1,016) | 822 (265-9,577) | | | |
| Rectal tissue (ng/g) | | 333 (256-1,034) | 1,004 (699-4,554) | 713 (615-1,377) | | | |

## 856 PHASE I TRIAL OF SUBCUTANEOUSLY ADMINISTERED VRC07-523LS AND PGT121

**Sharana Mahomed**[1], Nigel Garrett[1], Edmund Capparelli[2], Farzana Osman[1], Tanuja Gengiah[1], Derseree Archary[1], Cheryl Baxter[1], Penny Moore[3], Quarraisha Abdool Karim[1], Dan Barouch[4], Patricia E. Fast5, John R. Mascola[6], Julie E. Ledgerwood[6], Lynn Morris[3], Salim S. Abdool Karim[1]
*[1]Centre for the AIDS Programme of Research in South Africa, Durban, South Africa, [2]University of California San Diego, San Diego, CA, USA, [3]National Institute for Communicable Diseases, Johannesburg, South Africa, [4]Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston, MA, USA, [5]International AIDS Vaccine Initiative, New York, NY, USA, [6]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

**Background:** Effective, long-acting HIV prevention approaches are needed, especially for young women in Africa. We evaluated the safety and pharmacokinetics of monoclonal antibodies VRC07-523LS and PGT121 administered subcutaneously alone and in combination, as passive immunisation to young women in South Africa

**Methods:** CAPRISA 012A was a randomised,double-blinded, placebo-controlled, dose-escalation trial. Safety, tolerability, pharmacokinetics, serum neutralization activity and antidrug-antibody levels were assessed. 45 HIV-negative participants aged 18-40 years were randomised into 9 groups of 5 participants. In each group, 4 women were randomly assigned to the intervention and 1 to placebo. Study products were administered subcutaneously into the abdomen via needle and syringe with a maximum volume of 2mls per injection site. VRC07-523LS was administered at a dose of 5,10 or 20mg/kg once or at a repeat dose of 5 or 10 mg/kg at 12 or 24 weeks. PGT121 was administered at a dose of 3 and 10mg/kg once or at a repeat dose of 3 mg/kg at 12 weeks. VRC07-523LS at 5mg/kg and PGT121 at 3mg/kg were also administered in combination as two separate injections.

**Results:** The most common reactogenicity events were injection site tenderness and headaches. Nine related adverse events, that included proteinuria, elevated alanine aminotransferase and aspartate aminotransferase, were mild and transient. Median VRC07-523LS concentrations following 20mg/kg doses were 9.65µg/ml at 16 weeks and 3.86µg/ml at 24 weeks. VRC07-523LS PK profiles observed after administration of 5mg/kg were similar to those reported in the VRC605 trial conducted in the US. Median PGT121 concentrations after 3 and 10mg/kg doses were below the limit of quantitation in all participants after 8 weeks. Half-lives of VRC07-523LS and PGT121 were 29 and 20 days, respectively. When both VRC07-523LS and PGT121 were administered to participants, neutralisation profiles of the antibody combination were similar to neutralisation observed when each antibody was given alone. No antidrug-antibody responses were detected. All participants reported that they found the administration procedure acceptable and, if effective, were likely to recommend it to others.

**Conclusion:** VRC07-523LS and PGT121 administered subcutaneously individually and in combination at high doses were safe and well tolerated. Antibody levels suggest that subcutaneous administration of high dose VRC07-523LS is appropriate at 16 to 24-week dosing intervals while shorter intervals (<8 weeks) are appropriate for PGT121.

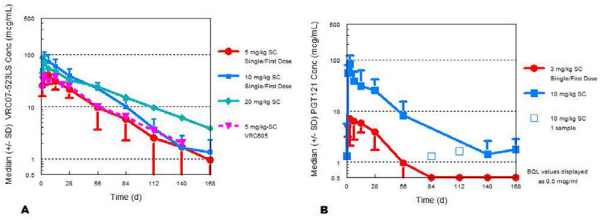



**Figure 1:** A) Observed median VRC07-523LS concentrations following 5, 10 and 20mg/kg subcutaneous administrations in the CAPRISA 012A trial and median concentrations following 5mg/kg subcutaneous administration in the VRC605 clinical trial. B) Observed median PGT121 concentrations following 3 and 10mg/kg subcutaneous administrations in the CAPRISA 012A trial.

## 857 A PHASE I CLINICAL TRIAL WITH A CONSENSUS SEQUENCE-BASED NATIVE-LIKE HIV-1 Env TRIMER

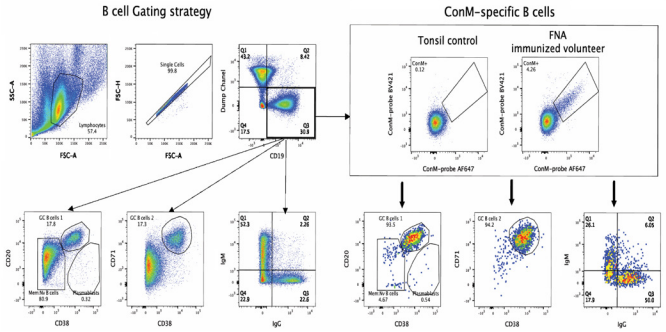
**Emma Reiss - Stafford**[1], Mathieu A. Claireaux[1], Karlijn van der Straten[1], Guistiniano V. Kerster[1], Wouter Olijhoek[1], Neeltje A. Kootstra[1], Rob Hurks[1], Antje Heit[2], Dietmar Katinger[3], Robin Shattock[4], Marit J. van Gils[1], Rogier W. Sanders[1], Godelieve De Bree[1]
*[1]Academic Medical Center, Amsterdam, Netherlands, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Polymun Scientific Immunbiologische Forschung GmbH, Klosterneuburg, Austria, [4]Imperial College London, London, UK*

**Background:** The HIV-1 envelope glycoprotein (Env) is the only target of antigen design for antibody-based vaccines. Inducing broadly neutralizing antibodies against the Env protein would be a major step towards having a prophylactic vaccine capable of curbing the HIV pandemic. The development of stabilized, native-like trimeric Env immunogens, such as SOSIP proteins, has advanced the HIV-1 vaccine field. ConM SOSIP.v7 (ConM) is a native-like HIV-1 Env trimer, based on an artificial consensus sequence of all HIV-1 isolates in group M, responsible for the pandemic. When used to immunize non-human primates, ConM induces strong autologous neutralizing antibody responses. We aim to evaluate the safety of ConM in humans, as well as explore its immunogenic properties and provide proof-of-concept of the utility of native-like Env trimers as components of an HIV-1 vaccine regimen.

**Methods:** The ACTHIVE-001 study is a single center, Phase I clinical trial at the Amsterdam UMC, the Netherlands (NCT03961438). 24 healthy participants are vaccinated with ConM at months 0, 2 and 6. Participants are randomized to receive either a consistent dose of vaccine, or a reduced booster dose at month 6, aimed to increase antibody responses and levels of somatic hypermutation. Safety information is solicited throughout a period of 18 months. Serological assays are performed, as well as lymph node fine needle aspirates (FNA) in order to investigate Env-specific germinal center (GC) responses. FNA samples are analyzed by nine colour flow-cytometry analysis.

**Results:** At present, 24 participants received an accumulated total of 51 vaccine administrations (current median follow-up 9 months), while 13 participants are not yet fully vaccinated. No Serious Adverse Events or Suspected Unexpected Serious Adverse Reactions were observed. The majority of Adverse Events were mild to moderate and self-limiting in nature. 27 lymph node FNA's were performed, with 20 yielding viable lymph node cells. In 11 (55 %) out of these procedures, ConM-specific B cells could be detected following one or two vaccinations. Strikingly, in some cases, > 90 % of ConM-specific B cells were GC B cells (Figure 1). Enrichment of ConM-specific B cells towards immunoglobulin G (IgG), compared to total B cells confirmed an isotype switch. Serological assays will be performed and correlated with FNA findings.

**Conclusion:** The ConM vaccine is safe when administered to humans and induces vaccine-specific germinal center reactions.




## 858 TAF/EVG DUAL-COMPARTMENT INSERT EFFICACY AGAINST RECTAL SHIV TRANSMISSION IN MACAQUES

**Natalia Makarova**[1], Tyana Singletary[1], M M. Peet[2], James Mitchell[1], Angela Holder[1], Chuong Dinh[1], Maria Mendoza[1], Yi Pan[1], Walid Heneine[1], Gerardo Garcia-Lerma[1], Meredith Clark[1], James Smith[1], Gustavo Doncel[2]
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]Eastern Virginia Medical School, Norfolk, VA, USA*

**Background:** Topical on-demand HIV prevention modalities are a desirable alternative to daily oral or long-acting injectable PrEP. CONRAD has developed inserts containing tenofovir alafenamide (TAF) and elvitegravir (EVG) for on-demand vaginal or rectal pericoital use, which are currently in early clinical testing. TAF/EVG inserts provided high protection as PrEP or PEP in pigtailed

macaques exposed vaginally to simian HIV (SHIV). We recently reported on the pharmacokinetics of the same inserts when applied rectally. Here, we assessed the efficacy of 1 or 2 inserts against rectal SHIV transmission in a repeat low-dose SHIV challenge model in pigtailed macaques.

**Methods:** Macaques were challenged rectally with low-dose SHIV162p3 4h after application of 1 or 2 TAF/EVG (20 mg/16 mg) inserts (n=6 per group). Single inserts and virus inoculums were placed at 4 cm from the anal sphincter. For 2 inserts, the second insert was placed 8 cm deep. Animals were challenged once weekly with SHIV162P3 for up to 10 weeks. Efficacy was estimated for 1 or 2 TAF/EVG inserts. Time to infection was compared to 6 placebo animals using the log rank test. Drug concentrations (EVG and TFV-DP) in rectal tissues were measured 4h after insert application by HPLC MS/MS.

**Results:** Median rectal tissue EVG and TFV-DP levels with 1 insert at 4h were 8128 ng/mg (range=BLQ–515,053) and 2187 fmol/mg (range=411–2500), respectively. With 2 inserts, EVG and TFV-DP were approximately one log higher compared with 1 insert (EVG 73,708 ng/mg; range BLQ–271,316 and TFV-DP 66,553 fmol/mg; range 2801–540,823). The single TAF/EVG insert arm was terminated after 6 exposures given the high rate of infection (4/6 infected at exposures 2, 3, 4, and 4). However, the time to infection was significantly delayed when compared to the placebo controls (p=0.0046). Calculated efficacy was 72.6% (95% exact CI =24.5%, 92.7%). With 2 inserts and 10 virus challenges, 2/6 animals became infected at exposures 2 and 8 resulting in 93.1% (95% CI=73.2%, 99.2%) efficacy (p=0.0022).

**Conclusion:** Despite similar tissue drug levels after vaginal and rectal application, a single TAF/EVG insert only achieved moderate protection after rectal challenge. Adding a second insert increased drug distribution through rectal tissues and boosted efficacy to 93%. Collectively, these data document pharmacodynamic differences between rectal and vaginal mucosa, informing insert dose selection in both compartments for advanced clinical development.

## 859 EXPECTATIONS OF PREVENTIVE BENEFITS & HIV-RELATED RISK BEHAVIORS IN HPTN069/ACTG5305

**Jeremy Sugarman**[1], Brian Weir[2], Chen Dun[2], Roy M. Gulick[3], Timothy Wilkin[3], Kenneth H. Mayer[4], Marybeth McCauley[5], Kevin P. Weinfurt[6]

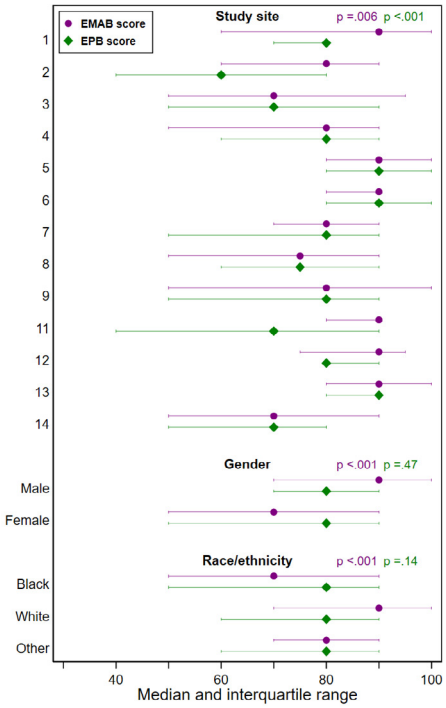
*[1]The Johns Hopkins University, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]Weill Cornell Medicine, New York, NY, USA, [4]The Fenway Institute, Boston, MA, USA, [5]FHI 360, Washington, DC, USA, [6]Duke University Medical Center, Durham, NC, USA*

**Background:** When clinical trial participants hold a preventive misconception (PM), i.e., expectations that experimental interventions will confer protection from HIV infection, they may engage in behaviors possibly increasing their risk of acquiring HIV. We evaluated these issues in HPTN069/ACTG A5305 [NCT01505114], a double-blind, Phase II study that compared 4 potential preexposure prophylaxis (PrEP) regimens: maraviroc (MVC); MVC + emtricitabine (FTC); MVC + tenofovir (TDF); and TDF + FTC. It enrolled at-risk cisgender men and cisgender and transgender women. At the time of the study there was clear evidence of preventive efficacy of FTC/TDF PrEP among men who have sex with men (MSM), but limited data for women, and no data about MVC.

**Methods:** Expectations of maximal aggregate benefit (EMAB) and personal benefit (EPB), which are key PM components, were measured at the week 40 study visit. Associations of EMAB and EPB with study site, self-reported gender, and race/ethnicity were evaluated using Kruskall-Wallis; associations with sexually transmitted infections (STIs), self-reported adherence, and condomless anal intercourse were evaluated with logistic regression with random intercepts for study site.

**Results:** Among participants with valid EMAB or EPB scores (n = 375), 65% were male, 35% female; 31% non-Hispanic Black, 41% non-Hispanic White, 20% Hispanic, and 7% other race/ethnicity. On a scale from 0 to 100, participants were on average 71.9% confident (SD = 25.1%) the medication(s) they received would prevent HIV infection (EPB); and thought on average, 76.6% (SD = 22.7%) of those on the most effective arm would have their chance of getting HIV reduced (EMAB). EMAB (p = .01) and EPB (p = .001) differed significantly across sites; EMAB varied significantly by race/ethnicity and gender, with non-Hispanic Whites and males having higher scores (Figure). Neither EMAB nor EPB was associated with STIs; a 20-point increase in EMAB was associated with 57% higher odds of condomless anal intercourse in the last 6 months (95% CI = 22% – 103%).

**Conclusion:** Despite the lack of evidence at the time for PrEP regimens besides TDF/FTC in MSM, average EMAB and EPB were high, but women had lower expectations of protection than men. Although PM is often considered to be a personal characteristic, we observed significant site differences despite using a common informed consent document that may indicate different messaging among sites or communities, which warrants careful future examination.




## 860 LONG-ACTING LENACAPAVIR PROTECTS AGAINST INTRAVENOUS CHALLENGE WITH SIMIAN-TROPIC HIV

Late Breaking

**Adrienne E. Swanstrom**[1], Bing Lu[2], Kelly Wang[2], Jim Zheng[2], Matthew W. Breed[1], Kristin E. Killoran[1], Joshua Kramer[1], Jorden L. Welker[1], Paul Bieniasz[3], Theodora Hatziioannou[3], Robert Gorelick[1], Wade Blair[2], Stephen Yant[2], Jeffrey D. Lifson[1], Gregory Q. Del Prete[1]

*[1]Frederick National Laboratory for Cancer Research, Frederick, MD, USA, [2]Gilead Sciences, Inc, Foster City, CA, USA, [3]The Rockefeller University, New York, NY, USA*

**Background:** The efficacy of daily oral pre-exposure prophylaxis (PrEP) to prevent HIV-1 infection is highly dependent on adherence. Lenacapavir (LEN) is a potent first-in-class HIV capsid (CA) inhibitor with long-acting pharmacokinetics (PK), making it attractive for PrEP. We previously derived a simian-tropic HIV-1 infectious molecular clone (stHIV-A19) that encodes HIV-1 CA and replicates to high titers in pigtail macaques (PTMs). Here we evaluate LEN in vitro potency against stHIV, and the PK and efficacy of subcutaneous (SC) LEN PrEP in PTMs against a high-dose intravenous (IV) stHIV challenge.

**Methods:** LEN in vitro potency against stHIV was evaluated in PTM PBMCs and adjusted for PTM plasma protein binding by competitive equilibrium dialysis. To assess LEN PK, naïve PTMs (n=6) each received two SC doses of LEN 6 weeks apart (15 mg/kg x 2, n=3; 50 mg/kg x 2, n=3). LEN plasma levels were measured by LC-MS. To evaluate LEN PrEP efficacy, naïve PTMs (n=10) each received a single IV challenge with stHIV (105 infectious units). The animals received a single SC injection of LEN (25 mg/kg, n=3) or vehicle (n=4) 30 days prior to challenge, or 7 daily SC injections of a 3-drug control regimen (tenofovir disoproxil fumarate/emtricitabine/dolutegravir) starting 3 days prior to challenge (n=3). Plasma stHIV RNA (vRNA) and stHIV DNA (vDNA) in PBMC were monitored longitudinally using sensitive qRT-PCR and qPCR assays, respectively.

**Results:** LEN showed potent anti-stHIV activity in PTM PBMCs, with a mean plasma protein-adjusted (pa)EC95 of 1.46 nM. In the PK study, plasma LEN concentrations peaked 3-4 weeks after the second LEN dose and declined slowly thereafter, with mean plasma LEN concentrations maintained above its paEC95 for >145 and >200 days after the second 15 mg/kg and 50 mg/kg dose, respectively. In the challenge study, mean plasma LEN concentrations exceeded target protective levels (4x paEC95) by day 1 post dose and at the time of challenge. There was no evidence of infection in any LEN or 3-drug group animals post IV challenge, with no detected plasma vRNA or PBMC vDNA through >8 months of follow-up. By contrast, all 4 placebo animals became

infected, with increasing plasma vRNA and PBMC vDNA first detected 4 days post IV challenge.

**Conclusion:** A single SC LEN injection effectively prevented stHIV infection in a stringent, high dose IV challenge model. These findings highlight the utility of the stHIV/PTM model and support the clinical development of long-acting LEN for PrEP.

## 861 EVALUATION OF THE COVID-19 CONTACT TRACING PROGRAM IN KING COUNTY, WA, USA

**Hannah N. Collins**[1], Matthew R. Golden[1], Rachel W. Kubiak[1], Tigran Avoundjian[1], Eli Kern[1], Elizabeth Meacham[1], Megan Baldwin[1], Sarah Stewart[1], Julia Hood[1]

[1]*Public Health–Seattle & King County, Seattle, WA, USA*

**Background:** Case investigation and contact tracing (CI/CT) is a key component of the response to COVID-19. CI/CT seeks to ensure that people exposed to SARS-CoV2 learn of their exposure and that infected persons and their contacts adhere to isolation and quarantine (I/Q) guidance. CI/CT programs also have the potential to address pandemic-related health inequities through the provision of support services. We evaluated the Public Health – Seattle & King County (PHSKC) CI/CT program, including its reach, timeliness, and case-reported impact on I&Q adherence.

**Methods:** The PHSKC CI/CT case interview assessed case demographics, recently visited places, contacts, and service needs. In March 2021, a random sample of cases completed an End of I&Q Survey to assess their adherence to I&Q guidance and opinions of CI/CT. We calculated descriptive statistics to evaluate survey and programmatic data collected between July 2020 and June 2021.

**Results:** The PHSKC CI/CT team interviewed 42,018 cases (81% of cases contacted) a mean of 6.1 days after symptom onset, and 3.4 days after SARS-CoV2 testing. Cases disclosed the names and addresses of 10,650 worksites (mean= 0.8/interview) and 11,269 other recently visited locations (mean= 0.5/interview), and provided contact information for 61,969 household members (mean=2.7/interview) and 8,753 non-household contacts (mean= 0.3/interview). The CI/CT team helped arrange COVID-19 testing for 5,660 contacts from 3,104 households, facilitated grocery delivery for 7,257 households, and referred 9,127 households for financial assistance. End of I&Q Survey participants (n=304, 54% of sampled) reported self-notifying an average of 4 non-household contacts and 69% agreed that the information and referrals provided by the CI/CT team helped them stay in isolation.

**Conclusion:** CI/CT reached many persons with COVID-19 and their household contacts and identified thousands of possible exposure venues. The intervention's effectiveness was likely limited by the inability to interview cases during their period of peak infectiousness and cases' reluctance to name non-household contacts, though cases notified many non-household contacts themselves. CI/CT was effective in linking people to testing, food, and financial assistance, and most cases reported that the intervention helped them isolate. These findings provide evidence that CI/CT can help mitigate the impact of COVID-19 on disproportionately impacted communities through the promotion of I&Q guidance and provision of support services.

**Disclosure of Contacts and Places Visited during COVID-19 Case Interview and Case-Initiated Exposure Notification, King County, WA, USA**

| | Interviewed Cases n/N (%) | Mean (sd) per case | Total number of contacts & venues reported: Unique (Total) |
|---|---|---|---|
| **Cases diagnosed July 2020-June 2021 who completed case interview with PHSKC (n=42018)** | | | |
| Disclosed actionable Information during PHSKC case interview for: | | | |
| Household member(s)[a] | 34132/41025 (83%)[b] | 2.69 (7.2) | 61969 |
| Non-household contact(s) | 4803/42018 (11%)[a] | 0.27 (1.1) | 8753 |
| Worksite(s) visited during exposure or infectious period[c] | 11061/14120 (78%)[b] | 0.81 (0.5) | 10650 (14826) |
| Non-worksite venue(s) visited during exposure or infectious period | 13359/42018 (32%)[b] | 0.46 (0.8) | 11269 (19508) |
| Prior to case interview, notified ≥1 employer of in person work attendance during infectious period | 12600/13532 (93%) | | |
| **Random Sample of PHSKC-Interviewed Cases Completing "End of IQ Survey" in March 2021 (n=304)** | | | |
| Notified all household members of their diagnosis[d] | 132/142 (93%) | | |
| Non-household contacts directly notified of exposure by case | 248/304 (82%) | 3.8 (7.1) | |

[a] Restricted to cases reporting 0 or more household contacts.
[b] Disclosed information for at least one contact or venue
[c] Restricted to cases with non-missing values
[d] Restricted to cases who reported to living with one or more people who had not been diagnosed with COVID-19.

## 862 WITHDRAWN

## 863 SARS-CoV-2 VACCINE EFFECTIVENESS FOR IN-HOSPITAL MORTALITY – ZAMBIA, 2021

**Jonas Hines**[1], Duncan Chanda[2], Peter Minchella[1], Sombo Fwoloshi[3], Megumi Itoh[1], Davies Kampamba[3], Khozya D. Zyambo[3], Suilanji Sivile[3], Francis D. Mwansa[3], Kennedy Malama[3], Simon Agolory[1], Lloyd B. Mulenga[3]

[1]*Centers for Disease Control and Prevention, Lusaka, Zambia,* [2]*University Teaching Hospital, Lusaka, Zambia,* [3]*Government of Zambia Ministry of Health, Lusaka, Zambia*

**Background:** Multiple vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have demonstrated high effectiveness for reducing severe COVID-19 and mortality. However, vaccine effectiveness data from the African region, where COVID-19 epidemiology and SARS-CoV-2 vaccine coverage differs from other regions, are limited. This study aimed to assess vaccine effectiveness in preventing in-hospital COVID-19 mortality in Zambia.

**Methods:** The study included patients hospitalized with SARS-CoV-2 infection at eight COVID-19 treatment centers across Zambia between May 1, 2021, and October 27, 2021, coinciding with the period of SARS-CoV-2 vaccine availability in Zambia. Patient's demographic and clinical information was collected, including vaccination status and in-patient disposition (discharged or died). The study used mixed-effects logistic regression to assess the odds of in-hospital mortality by vaccination status, adjusted for age, sex, number of comorbid conditions, disease severity, and COVID-19 treatment center (random-effects term). Vaccine effectiveness was defined as 1 minus the adjusted odds ratio (aOR) times 100%.

**Results:** During the study period for Zambia, 729 patients ≥18 years being treated in one of the participating COVID-19 treatment centers had data describing their hospitalization course and SARS-CoV-2 vaccination status. Forty-eight (6.6%) patients had received ≥1 vaccine dose at the time they were admitted to the hospital. Forty-two (87.5%) received AstraZeneca, three (6.3%) received Janssen, and three (6.3%) were unknown vaccine type. Only five (11.9%) of AstraZeneca recipients had received two vaccine doses. The age and sex of vaccinated patients was not different than unvaccinated patients (median age 60 years vs. 57 years, respectively, p=0.6; 50.0% females vs. 42.9% females, respectively, p=0.4). In-hospital mortality was 16.7% for patients reporting ≥1 vaccine dose and 32.0% for unvaccinated patients (aOR: 0.3 [95% confidence interval (CI): 0.1-0.7). SARS-CoV-2 vaccine effectiveness for in-hospital mortality was 65.8% (95% CI: 25.9–85.9%).

**Conclusion:** Consistent with evidence from other countries, vaccinated patients demonstrated lower odds of in-hospital mortality than those who

were unvaccinated in Zambia. The low vaccine coverage in Zambia and among patients in this study likely impacted the precision of the estimate for the odds of in-hospital mortality. Vaccination is a critical tool for reducing the consequences of the SARS-CoV-2 epidemic in Zambia.

## 864 STOPCoV: SAFETY AND EFFICACY OF PREVENTATIVE COVID VACCINES

**Sharon Walmsley**[1], Leah Szadkowski[1], Rosemarie Clarke[1], Rizani Ravindran[1], Anne-Claude Gingras[2]

*[1]University Health Network, Toronto, Canada, [2]Lunenfeld-Tanenbaum Research Institute, Sinai Health, Toronto, Canada*

**Background:** In attempts to rapidly immunize a greater proportion of the Ontario population against COVID, public health officials recommended extending the interval between vaccine doses and allowed "mixing of vaccine types". The impact of these decisions on the antibody response to the vaccine, particularly in the community dwelling elderly population is unknown.

**Methods:** The STOPCoV study is designed to compare the IgG antibody response to spike protein and receptor binding domain (RBD) after COVID vaccination in those aged ≥ 70 years relative to a cohort aged 30-50 years. This prospective decentralized observational study is conducted remotely on a digital platform (www.stopcov.ca). Participants signed an e-consent, completed questionnaires and will submit dried blood spot (DBS) specimens 6-8 times over 48 weeks after the second vaccine dose. DBS samples were analyzed for IgG antibodies to spike and RBD by an in-house ELISA. We report here the ratio-normalized levels of anti-spike and anti-RBD IgG antibodies prior to and at 2 weeks after the second vaccine with comparisons between age groups. Linear regression models were used to determine the effect of age on the ratio normalized RBD antibody levels 2 weeks post second dose of vaccine after adjusting for potential confounders determined a priori.

**Results:** 1286 persons enrolled between May 17 and July 31, 2021. 1194 participants (853 > 70 years; 341 aged 30-50) completed at least one study related task. 761 (64.1%) are female. Most received an mRNA vaccine, with 863 (74%) receiving the same vaccine brand, and 196 (17%) receiving mixed brands over 2 doses. Two weeks after the second vaccine dose, the median interquartile rangeanti-spike antibody level was 0.76 [0.45, 1.16] for those ≥70 compared to 1.3 [0.98, 1.56] for those 30-50 (p<0.001). The median anti-RBD antibody levels were 0.28 [0.15, 0.53] and 0.66 [0.41, 1.08] (p<0.001) for the older and younger cohorts respectively. After adjusting for gender, cardiovascular disease, cancer, diabetes, transplant or immune suppression, body mass index, vaccine brand, and time between doses, participants ≥70 had lower levels of anti-RBD antibodies at 2 weeks after 2nd dose (β=-0.14, 95% confidence interval -0.19, -0.08, p<0.0001).

**Conclusion:** High antibody levels against COVID-19 are attainable after 2 doses of mRNA vaccines. Levels were higher with Moderna than Pfizer. Delay of the second dose to 4 months or mixing of brands had minimal impact on the antibody level but levels are lower in the elderly.

**Linear Regression Model of 2-week after 2nd Dose RBD Antibody**

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | β (95%CI) | p | β (95%CI) | p |
| Female | 0.076 (0.033, 0.12) | <0.001 | 0.046 (0.0061, 0.087) | 0.02 |
| Age 70+ | -0.23 (-0.27, -0.18) | <0.0001 | -0.14 (-0.19, -0.084) | <0.0001 |
| Cardiovascular Disease | -0.087 (-0.13, -0.045) | <0.0001 | -0.011 (-0.056, 0.034) | 0.64 |
| Cancer History | -0.11 (-0.17, -0.059) | <0.0001 | -0.062 (-0.12, -0.0092) | 0.02 |
| Diabetes | -0.056 (-0.12, 0.012) | 0.1 | -0.011 (-0.077, 0.055) | 0.75 |
| BMI Category | | | | |
| Under/Healthy Weight (BMI<25) | Ref. | | Ref. | |
| Overweight (BMI 25-30) | -0.021 (-0.068, 0.026) | 0.37 | 0.015 (-0.029, 0.059) | 0.5 |
| Obese (BMI≥30) | 0.054 (0.00056, 0.11) | 0.05 | 0.063 (0.012, 0.11) | 0.01 |
| Vaccine Type | | | | |
| Pfizer x2 | Ref. | | Ref. | |
| Moderna x2 | 0.2 (0.13, 0.26) | <0.0001 | 0.14 (0.075, 0.2) | <0.0001 |
| Pfizer x1, Moderna x1 | 0.16 (0.11, 0.22) | <0.0001 | 0.14 (0.089, 0.19) | <0.0001 |
| AstraZeneca x1, Pfizer/Moderna x1 | 0.13 (0.043, 0.21) | <0.01 | 0.077 (-0.0049, 0.16) | 0.07 |
| ≥8 Weeks Between Doses | -0.2 (-0.24, -0.15) | <0.0001 | -0.1 (-0.15, -0.051) | <0.0001 |

## 865 PROPORTION OF PLWH NOT VACCINATED FOR COVID-19 IN ITALY AND PREDICTORS

**Alessandro Tavelli**[1], Stefania Cicalini[2], Diletta Barbanotti[3], Spinello Antinori[3], Daniela Segala[4], Giovanni Guaraldi[5], Marta Guastavigna[6], Claudia Lazzaretti[7], Massimo Puoti[8], Francesca Ceccherini-Silberstein[9], Antonella Castagna[10], Enrico Girardi[2], Antonella D'Arminio Monforte[3], Andrea Antinori[2]

*[1]Icona Foundation, Milan, Italy, [2]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [3]University of Milan, Milan, Italy, [4]University of Ferrara, Ferrara, Italy, [5]University of Modena and Reggio Emilia, Modena, Italy, [6]Amedeo di Savoia Hospital, Torino, Italy, [7]Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, [8]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, [9]University of Rome Tor Vergata, Rome, Italy, [10]San Raffaele Scientific Institute, Milan, Italy*

**Background:** The vaccination campaign against COVID-19 has a substantial beneficial public health impact, but vaccine hesitancy or issues to the access to vaccine could undermine the efforts made. We aim to determine the proportion of people living with HIV (PLWH) not vaccinated for COVID-19 in a cohort of PLWH in Italy and identify predictors of missing vaccination.

**Methods:** Cross sectional study conducted in the Icona network. All PLWH of the centers participating the study with at least 1 follow-up in 2020-2021 were included. Their vaccination status for COVID-19 has been evaluated till 08Oct2021, before entering in the 3rd booster dose campaign for fragile populations in Italy. Data on vaccination status have been collected by medical records and/or administrative databases. Descriptive statistics, crude and adjusted logistic regression models for identifying predictors of not being vaccinated (0 doses received) were used.

**Results:** Vaccination status has been assessed for 3,242 subjects from 17 centers of the cohort. 319/3,242 resulted still not vaccinated (9.8%) and 2,923 received at least one dose (90.2%). The full cycle has been completed by 2,732 subjects (85.5%). 89.1% of PLWH received a mRNA vaccine, 6.6% a viral vector and 4.3% unknown. Characteristics of patients according to being vaccinated or not are shown in Table 1A. In the adjusted logistic regressions, PLWH who did not receive the vaccine were more frequently younger (per 10 years younger AOR=1.22, 95%CI 1.07-1.38), and current/ex injecting drug users (IDU) (AOR=1.61, 95%CI 1.01-2.57), while having a current HIV-RNA < 50 copies mL (AOR=0.62, 95%CI 0.44-0.89), no previous diagnosis of COVID-19 (AOR=0.52, 95%CI 0.30-0.92) and being MSM (AOR=0.63, 95%CI 0.46-0.86) had lower risk to miss vaccination.

**Conclusion:** The acceptance and uptake of vaccine among PLWH has been high, with a proportion of patients who completed the full vaccination cycle higher than targeted general population in Italy (85.5% vs 78.3% at W40-2021). Access to vaccination has been favourable for PLWH but some challenges remain for IDU/ex-IDU PLWH. The vaccination hesitancy lasts in younger population. MSMs seem to have a stronger attitude to protection, whereas patients with unsuppressed HIV-RNA could have a lower compliance reflected also in a lower COVID-19 vaccine uptake. Some selection bias on the population in analysis cannot be ruled out. These findings could help to develop interventions for increasing vaccination uptake for PLWH in future.

**Table 1A. Patients' characteristics**

| | Vaccine not executed | | Vaccine Executed | | p | Total | |
|---|---|---|---|---|---|---|---|
| | n=319 | 9.8% | n=2923 | 90.2% | | n=3242 | 100.0% |
| **Sex, Male, n(%)** | 243 | 76.2% | 2421 | 82.8% | 0.003 | 2664 | 82.2% |
| **Age, years, median(IQR)** | 45 | 35-53 | 48 | 39-56 | <0.001 | 48 | 39-56 |
| **Italian, n(%)** | 226 | 70.8% | 2434 | 83.3% | <0.001 | 2660 | 82.0% |
| **Year HIV Diagnosis, median(IQR)** | 2016 | 2011-2019 | 2014 | 2009-2018 | <0.001 | 2014 | 2009-2018 |
| **Mode of HIV Tranmission, n(%)** | | | | | 0.001 | | |
| Heterosexual contacts | 144 | 45.1% | 1043 | 35.7% | | 1187 | 36.6% |
| IDU | 33 | 10.3% | 239 | 8.2% | | 272 | 8.4% |
| MSM | 134 | 42.0% | 1532 | 52.4% | | 1666 | 51.4% |
| Other/Unknown | 8 | 2.5% | 109 | 3.7% | | 117 | 3.6% |
| **Nadir CD4, cells/mmc, median(IQR)** | 291 | 123-431 | 288 | 146-420 | 0.892 | 289 | 144-242 |
| **Nadir CD4 <200 cells/mmc, n(%)** | 108 | 33.9% | 955 | 32.7% | 0.839 | 1063 | 32.8% |
| **AIDS, n(%)** | 42 | 13.2% | 414 | 14.2% | 0.627 | 456 | 14.1% |
| **Education, n(%)** | | | | | <0.001 | | |
| Middle School/Elementary | 77 | 24.1% | 705 | 24.1% | | 782 | 24.1% |
| University/High School | 110 | 34.5% | 1382 | 47.3% | | 1492 | 46.0% |
| Unknown | 132 | 41.4% | 836 | 28.6% | | 968 | 29.9% |
| **Current CD4, cells/mmc, median(IQR)** | 641 | 423-840 | 696 | 507-930 | <0.001 | 689 | 499-924 |
| **Current CD4<200 cells/mmc, n(%)** | 24 | 7.5% | 115 | 3.9% | 0.010 | 139 | 4.3% |
| **Current HIV-RNA> 50 copies/ml, n(%)** | 58 | 18.2% | 267 | 9.1% | <0.001 | 325 | 10.0% |
| **Charlson Comorbidity Age-adjusted median(IQR)** | 0 | 0-2 | 1 | 0-3 | <0.001 | 1 | 0-3 |
| **At least 1 comorbidity*, n(%)** | 75 | 23.5% | 950 | 32.5% | 0.001 | 1025 | 31.6% |
| **Previous COVID-19 diagnosis** | | | | | <0.001 | | |
| No | 111 | 34.8% | 1385 | 47.4% | | 1496 | 46.1% |
| Yes | 17 | 5.3% | 113 | 3.9% | | 130 | 4.0% |
| Unknown | 191 | 59.9% | 1425 | 48.7% | | 1616 | 49.9% |
| **Vaccine Type (1st dose)** | | | | | . | | |
| mRNA-1273 | . | . | 1019 | 34.9% | | . | . |
| BNT162b2 | . | . | 1585 | 54.2% | | . | . |
| Ad26.COV2.S | . | . | 46 | 1.6% | | . | . |
| ChAdOx1 | . | . | 146 | 5.00% | | . | . |
| Unknwon | . | . | 127 | 4.3% | | . | . |

**Comorbidities considered: Myocardial infarction, Congestive Hearth, Failure Peripheral vascular disease, Cerebrovascular accident, Dementia, COPD, Connective tissue or autoimmune disease, Peptic ulcer, Liver disease (severe or mild), Diabetes mellitus, Hemiplegia, CKD, Solid tumor, Leukemia, Lymphoma, Arterial Hypertension*

## 866 EFFECTIVENESS OF COVID-19 VACCINATION AMONG PEOPLE LIVING WITH HIV DURING AN OUTBREAK

**Kuan-Yin Lin**[1], Pei-Ying Wu[1], Wang-Da Liu[1], Hsin-Yun Sun[1], Chien-Ching Hung[1], Shan-Chwen Chang[1]

*[1]National Taiwan University Hospital, Taipei, Taiwan*

**Background:** A large-scale community COVID-19 outbreak occurred between April and August 2021 in Taiwan, where non-pharmaceutical interventions (NPIs) have been strictly implemented and COVID-19 vaccination program was not implemented until 1 March, 2021. Although COVID-19 vaccination is recommended for at-risk populations, the vaccine effectiveness in people living with HIV (PLWH) remains incompletely understood. We evaluated the effectiveness of COVID-19 vaccination among PLWH during a COVID-19 outbreak in Taiwan.

**Methods:** From 1 March to 30 September, 2021, all adult PLWH without previous SARS-CoV-2 infection were included and advised to receive 2 doses of COVID-19 vaccine. The government-funded vaccination campaign provided different types of COVID-19 vaccine, including ChAdOx1 nCoV-19 (AZD1222), BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and MVC-COV1901 (Medigen) vaccines. The primary endpoint of this study was the vaccine effectiveness in preventing COVID-19 among PLWH, which was estimated by comparing incidence rates between the unvaccinated, partially vaccinated, and fully vaccinated groups in a dynamic cohort.

**Results:** During the study period, 3131 PLWH were included, with 99.9% on antiretroviral therapy, 99.8% being MSM and median CD4 count of 627 cells/$mm_3$. In the dynamic cohort, 3128 PLWH contributed 516892 person-days of follow-up (PDFU) to the unvaccinated group, 2476 PLWH contributed 139163 PDFU to the partially vaccinated group, and 236 PLWH contributed 12011 PDFU to the fully vaccinated group (Table). During the follow-up, 37 PLWH (1.2%) acquired SARS-CoV-2 infections. The incidence rate of SARS-CoV-2 infection was 6.4 per 100,000 PDFU in the unvaccinated group, which decreased to 2.9 and 0 per 100,000 PDFU in the partially and fully vaccinated groups, respectively. The adjusted incidence rate ratios were 0.47 (95% CI, 0.17-1.32) in the partially vaccinated group and <0.01 in the fully vaccinated group compared with the unvaccinated group, resulting in vaccine effectiveness rates of 53.4% and 99.9% for single- and 2-dose COVID-19 vaccination, respectively.

**Conclusion:** COVID-19 vaccination was clinically effective among PLWH during the outbreak setting where NPIs were strictly implemented.

**Table. Baseline characteristics of the PLWH who contributed follow-up periods**

| Characteristic | Unvaccinated group (n=3128)[a] | Partially vaccinated group (n=2476) | Fully vaccinated group (n=236) | *P* value |
|---|---|---|---|---|
| Age, median (IQR), years | 41 (35-50) | 41 (35-50) | 41 (34-50) | 0.470 |
| Male sex, n (%) | 3121 (99.8) | 2472 (99.8) | 236 (100) | 0.688 |
| Baseline CD4 count, median (IQR), cells/mm$^3$ | 625 (467-809) | 635 (478-825) | 587 (463-779) | 0.163 |
| Baseline PVL, median (range), $log_{10}$ copies/mL | UD (UD-6.23) | UD (UD-6.23) | UD (UD-5.77) | 0.841 |
| PVL <20 copies/mL, n (%) | 2592 (82.9) | 2080 (84.0) | 205 (86.9) | 0.195 |
| Types of vaccine, n (%) | | | | |
| ChAdOx1 nCoV-19 | NA | 1744 (70.4) | 169 (71.6) | 0.712 |
| mRNA-1273 | NA | 592 (23.9) | 36 (15.3) | 0.003 |
| MVC-COV1901 | NA | 110 (4.4) | 4 (1.7) | 0.044 |
| BNT162b2 | NA | 11 (0.4) | 10 (4.2) | <0.001 |
| Others[b] | NA | 18 (0.7) | 17 (7.2) | <0.001 |

Abbreviations: IQR, interquartile range; NA, not available; PLWH, people living with HIV; PVL, plasma HIV RNA load; UD, undetectable.
[a]Three PLWH had received COVID-19 vaccination at least 14 days before 1 March, 2021, for which they did not contribute follow-up periods in the unvaccination group.
[b]PLWH received Sinovac and Sinopharm COVID-19 vaccines in China.

## 867 TENOFOVIR DISOPROXIL FUMARATE AND SEVERITY OF COVID-19 IN PEOPLE WITH HIV INFECTION

**Julia Del Amo**[1], Rosa Polo[1], Santiago Moreno[2], Esteban Martinez[3], Alfonso Cabello Úbeda[4], José A. Iribarren[5], Adrià Curran[6], Juan Macias[7], Marta Montero[8], Carlos Dueñas[9], Ana Mariño[10], Asun Diaz[11], Jose R. Arribas[12], Inma Jarrín[11], Miguel Hernán[13]

*[1]Ministry of Health, Spain, Madrid, Spain, [2]University Hospital Ramón y Cajal Madrid, Spain, Madrid, Spain, [3]Hospital Clinic of Barcelona, Barcelona, Spain, [4]Fundacion Jimenez Diaz, Madrid, Spain, [5]Hospital Donostia, San Sebastián, Spain, [6]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [7]Hospital Universitario de Valme, Seville, Spain, [8]Hospital Universitario La Fe, Valencia, Spain, [9]University Clinical Hospital of Valladolid, Valladolid, Spain, [10]Ferrol University Hospital, Ferrol, Spain, [11]Institute of Health Carlos III, Madrid, Spain, [12]La Paz University Hospital, Madrid, Spain, [13]Harvard TH Chan School of Public Health, Boston, MA, USA*

**Background:** Effective, safe, and affordable antivirals are needed for COVID-19. Several lines of reseach suggest that tenofovir may be effective against COVID-19 but no large-scale human studies with appropriate adjustment for comorbidities have been conducted. We describe the incidence, clinical severity and mortality of laboratory-confirmed SARS-CoV-2 infection by antiretroviral therapy (ART) among HIV-positive individuals with virological control adjusting for key potential confounders including hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.

**Methods:** We studied HIV-positive individuals on ART in 2020 at 69 HIV clinics in Spain from February 1 to December 31. These 69 clinics serve approximately 44% of all persons on ART with virological suppression in Spain. We collected data on sociodemographics, ART, CD4-cell count, HIV-RNA viral load, comorbidities and the following outcomes: laboratory-confirmed SARS-CoV-2 infection, COVID-19 hospitalization, intensive care unit (ICU) admission and death. We compared 48-week risks, relative risks, relative differences and 95% confidence intervals (CI) for individuals receiving tenofovir disoproxyl fumarate (TDF)/emtricitabine (FTC), tenofovir alafenamide (TAF)/ FTC, abacavir (ABC)/ lamivudine (3TC), and other regimes. All estimates were adjusted for clinical and sociodemographic characteristics via inverse probability weighting.

**Results:** Of 51,558 eligible individuals, 39.6% were on TAF/FTC, 11.9% on TDF/FTC, 26.6% on ABC/3TC, 21.8% on other regimes. There were 2,402 documented SARS-CoV-2 infections (425 hospitalizations, 45 ICU admissions, 37 deaths). Compared with TAF/FTC, the estimated risk ratios (RR) (95% CI) of hospitalization were 0.66 (0.43, 0.91) for TDF/FTC and 1.29 (1.02, 1.58) for ABC/3TC, the RRs of ICU admission were 0.28 (0.11, 0.90) for TDF/FTC and 1.39 (0.70, 2.80) for ABC/3TC, and the RRs of death were 0.37 (0.23, 1.90) for TDF/FTC and 2.02 (0.88-6.12) for ABC/3TC. The corresponding RRs of hospitalization for TDF/FTC were 0.49 (0.24, 0.81) in individuals ≥50 years and 1.15 (0.59, 1.93) in younger individuals.

**Conclusion:** Our findings suggest that, compared with other antiretrovirals, TDF/FTC lowers COVID-19 severity among HIV-positive individuals with virological control. This protective effect may be restricted to individuals aged 50 years and older. Confirmatory randomized trials of TDF/FTC for the prophylaxis and early treatment of COVID-19 are warranted.

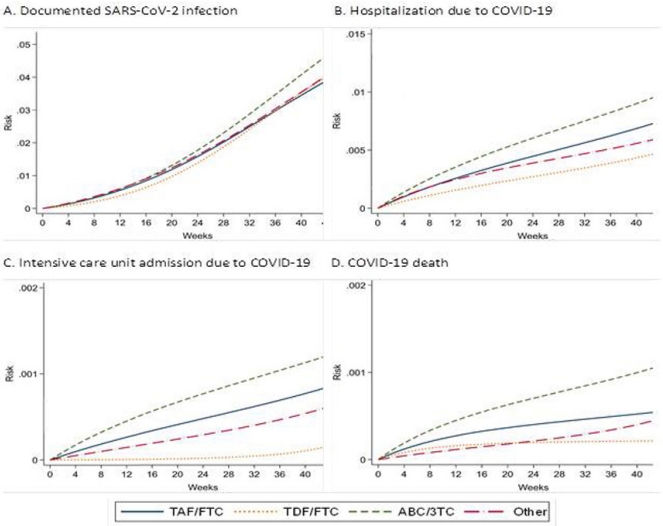



Figure. Estimated risks of COVID-19 outcomes by NRTI combination in HIV-positive individuals, *CoVIHd Study, Spain, February-December 2020. * Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), CD4 (<350, 350-500, >500 cells/mm3), and hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.

## 868 HUMORAL IMMUNE RESPONSE AFTER COVID-19 VACCINATION IN PEOPLE LIVING WITH HIV

Late Breaking

**Linda Wittkop**[1], Paul Loubet[2], Mathieu Chalouni[1], Karine Lacombe[3], Valérie Pourcher[3], Alain Makinson[4], Pierre-Olivier Girodet[1], David Chirio[5], Maeva Lefebvre[6], Catherine Mutter[7], Xavier De Lamballerie[8], Julie Longobardie[1], Axel Levier[9], Jean-Daniel Lelièvre[10], Odile Launay[11]

*[1]University of Bordeaux, Bordeaux, France, [2]University of Montpellier, Montpellier, France, [3]Sorbonne University, Paris, France, [4]Centre hospitalier universitaire Montpellier, Montpellier, France, [5]Centre Hospitalier Universitaire de Nice, Nice, France, [6]Centre Hospitalier Universitaire de Nantes, Nantes, France, [7]Hopitaux*

*universitaire de Strasbourg, Strasbourg, France, [8]Aix-Marseille Université, Marseille, France, [9]ANRS Maladies Infectieuses Emergentess, Paris, France, [10]Université Paris Est Créteil, Paris, France, [11]Assistance Publique–Hôpitaux de Paris, Paris, France*

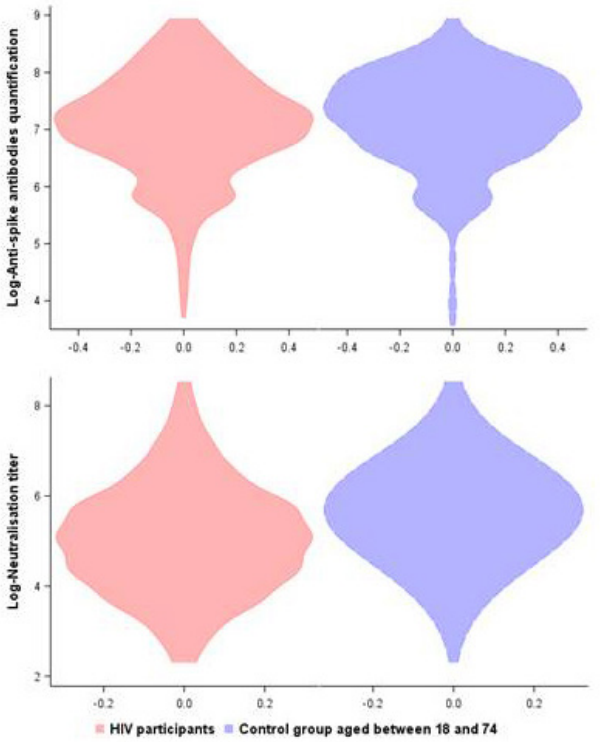
**Background:** High effectiveness of COVID-19 vaccines was demonstrated. In people living with HIV (PLWHIV), immunogenicity and efficacy of COVID-19 vaccines might be lower. We evaluated the humoral immune response to COVID-19 vaccines in PLWHIV compared to controls without specific comorbidities.

**Methods:** PLWHIV and controls from the French national multi-center prospective COVID 19 vaccine cohort study ANRS0001S COV-PopART were included. Participants with pre-vaccination positive SARS CoV-2 antibodies, history of SARS CoV-2 infection, or positive SARS CoV-2 anti-nucleocapsid (NCP) antibodies were excluded. Percentage (95% confidence interval (CI)) of responders, geometric means (95% CI) of anti-Spike SARS-CoV-2 IgG antibodies (ELISA) and specific neutralizing antibodies (in vitro neutralization assay) were estimated one month after the second vaccine dose. Serological tests (ELISA Euroimmun) with tests limits and seroneutralization for the original SARS-CoV-2 strain were performed centrally.

**Results:** Among the 6089 participants included, 2625 were PLWHIV or controls; 1212 had serological measures available one month after their second dose and 1133 had negative anti-NCP antibodies: 591 PLWHIV and 542 controls. PLWHIV were older than controls: 56.5 years, (51.2-62.2) vs 52.1 years (42.1-62.6) and more frequently male (78.7% vs 52.1%). All PLWHIV were under antiretroviral therapy, 76% had an undetectable viral load and 70.6% had CD4 counts above 500 cells/mm$_3$. Participants had primarily received BNT162b2 (92.4% in PLWHIV vs 88.2% in controls). Proportions of participants who developed anti-Spike IgG (98.5% [97.1; 99.3] vs 100.0% [99.3; 100.0], p<0.01) and neutralizing antibodies (96.8% [95.0; 98.1] vs 99.8 [99.0; 100.0], p<0.01) were significantly lower in PLWHIV compared to controls. Of the nine non-responding PLWHIV, all were in CDC stage C, two had detectable HIV viral load and seven had CD4 cell counts below 200/mm$_3$. PLWHIV had similar levels of anti-Spike antibodies (1149.0 [1066.6; 1237.8] vs 1299.3 [1208.7; 1396.6] BAU/mL, p=0.27) but lower seroneutralization titers (156.8 [141.9; 173.2] vs 279.8 [256.1; 305.6] IU/mL, p<0.01) than controls (figure).

**Conclusion:** PLWHIV under ARV treatment had high response rates one month after two doses of COVID-19 vaccination. Nonetheless, seroneutralization titers were lower, and non-responders in PLWHIV had a more advanced disease stage. Longer follow-up is needed to gain a better insight into the humoral response after COVID-19 vaccination in PLWHIV.

Figure : Violin plots of log anti-spike antibody and log seroneutralization quantifications




**869** **TRENDS IN STI SCREENING DURING COVID-19 AND MISSED CASES AMONG ADOLESCENTS**

New Investigator Scholar

**Stephen Bonett**[1], Daniel Teixeira da Silva[1], Danielle Petsis[2], Jungwon Min[2], Spandana Makeneni[2], Anjali Mahajan[1], Sarah M. Wood[2]
*[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Children's Hospital of Philadelphia, Philadelphia, PA, USA*

**Background:** Sexually transmitted infection (STI) diagnosis serves as an important linkage to HIV testing and pre-exposure prophylaxis (PrEP) for adolescents. The COVID-19 pandemic disrupted sexual health services for young people, with a potential consequence of increasing undiagnosed STIs. This study aimed to describe STI testing changes and estimate undiagnosed STI cases during the pandemic.

**Methods:** We analyzed electronic medical records for chlamydia, gonorrhea, and trichomonas testing encounters from six pediatric primary care clinics in Philadelphia, July 2014-November 2020. We assessed whether testing was asymptomatic screening, risk-based testing, or symptomatic testing, and whether any result was positive. We evaluated STI trends over time, comparing pre-pandemic (before March 1st, 2020) and pandemic periods (after March 1st, 2020). Missed STI cases during the pandemic were estimated using decreases in patient volume and asymptomatic screening as compared to the previous year. Generalized linear mixed-effects models estimated the effects of patient-level and neighborhood-level characteristics on STI outcomes.

**Results:** 35,548 STI testing encounters were analyzed, including 2,958 during the pandemic period. The median patient age was 17.5 years, 57% of patients were female, and 84% were Black/African American. Mean monthly STI testing encounters decreased from 479/month pre-pandemic to 329/month during the pandemic. Test positivity increased from 12.5% pre-pandemic to a peak of 27.5% in April 2020. The percent of STI tests performed as asymptomatic screening dropped from 72.5% pre-pandemic to a nadir of 54.5% in April 2020 (Figure). We estimate that the decrease in asymptomatic screening in the pandemic period would be associated with 159 missed cases (23.8% of expected cases) based on patient volume from the previous year. In multivariate models controlling for testing type (asymptomatic screening, risk-based testing, or symptomatic testing), the odds of test positivity were 50% higher during the pandemic (OR: 1.50, p<0.001).

**Conclusion:** STI test positivity increased during the pandemic while asymptomatic screening decreased. Test positivity was higher for asymptomatic patients, suggesting increased STI prevalence. These changes likely resulted in a substantial number of undiagnosed STIs, representing missed opportunities for PrEP linkage. Efforts are needed to re-establish and sustain access to STI services for adolescents in response to disruptions caused by the pandemic.

**870** **STI TRANSMISSION DYNAMICS DURING THE COVID-19 PANDEMIC AMONG URBAN SEXUAL MINORITIES**

**Christina Schumacher**[1], Nicole Thornton[1], Jessica Duchen[1], Carla Tilchin[1], Khalil Ghanem[1], Matthew M. Hamill[1], Carl Latkin[2], Anne Rompalo[1], Sebastian Ruhs[3], Adena Greenbaum[4], Jacky Jennings[1]
*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]Chase Brexton Health Services, Baltimore, MD, USA, [4]Baltimore City Health Department, Baltimore, MD, USA*

**Background:** The impact of COVID-19 mitigation measures on STI transmission and racial disparities remains unknown. The objectives were to examine trends in sex and drug risk behaviors, access to sexual health services and STI positivity overall and by race during- compared to pre-pandemic among urban sexual minorities (MSM).

**Methods:** Sexually-active MSM aged 18-45 years were administered a behavioral survey and STI testing at three-month intervals. Participants completing > one during-pandemic (April- December 2020) and one pre-pandemic study visit (before March 13, 2020) occurring < six months apart were included. Generalized estimating equations with modified Poisson regression models compared outcomes during- compared to pre-pandemic visits.

**Results:** Among 231 MSM, reports of > three sex partners declined [adjusted Prevalence Ratio (aPR): pandemic-1(p1) 0.68, 95% CI (0.54-0.86); pandemic-2(p2) 0.65 (0.51-0.84); pandemic-3(p3) 0.57 (0.43-0.75)]; similar findings were observed among Black and non-Black MSM. Black, but not non-Black MSM, reported sustained decreases in substance use (aPR: p1 0.90 (0.79-1.03); p2 0.74 (0.62-0.89); p3 0.82 (0.67-0.99)], and increased HIV/PrEP care engagement [aPR: p1 1.20 (1.07-1.34); p2 1.24 (1.11-1.39); p3 1.30 (1.16-1.47)]. Reported STI testing

(overall and by race) decreased [aPR: p1 0.68 (0.57-0.81); p2 0.78 (0.67-0.92)], then rebounded [aPR: p3 1.01 (0.87-1.18)]. Overall, neither chlamydia [aPR: p2 1.62 (0.75-3.46); p3 1.13 (0.24-1.27)] nor gonorrhea [aPR: p2 0.87 (0.46-1.62) p3 0.56 (0.24-1.27)] positivity significantly changed during vs. pre-pandemic.
**Conclusion:** We observed sustained decreases in STI risk behaviors but minimal change in STI positivity during compared to pre-pandemic. Findings underscore the urgent need for novel strategies to deliver STI prevention services without in-person interactions among MSM.

## 871 WITHDRAWN

## 872 SEXUAL HEALTH CLINIC OUTCOMES AND PrEP LINKAGE IN A LARGE URBAN EMERGENCY DEPARTMENT

**Aniruddha Hazra**[1], Ruby Massey[1], Michelle Moore[1], Damaris Garcia[1], Richard Rodgers[1], Jessica Schmitt[1]
[1]*University of Chicago, Chicago, IL, USA*

**Background:** Due to the closure of surrounding city-run sexually transmitted infection (STI) clinics, uninsured and underinsured patients living near an urban academic medical center have been relying on the Emergency Department (ED) for their sexual health needs. A novel Sexual Wellness Clinic (SWC) was created in February 2019 to provide comprehensive sexual health care to provide linkage to Pre-Exposure Prophylaxis (PrEP), primary care, and other essential services.
**Methods:** SWC patients were identified in the ED or after being notified of a positive STI result from the ED and scheduled into clinic. Once at the SWC, patients underwent a complete history and physical examination, comprehensive STI testing, and, if indicated, empiric treatment as well as same-day initiation of Pre-Exposure Prophylaxis (PrEP). Social services within the clinic also assisted in arranging primary care follow-up either at the medical center or an affiliated Federally Qualified Health Center (FQHC). We retrospectively reviewed outcomes and rates of PrEP prescription among SWC patients.
**Results:** From 2/20/2019 to 9/30/2021, SWC served 560 unique patients, 50.5% (n= 283) were cismen and 49.5% (n= 277) were ciswomen. The majority of patients were African American (93.4%, n=523), non-Hispanic or Latinx (96.1%, n=538), between 18 to 29 years old (62.3%, n=350), and had Medicaid or were uninsured (84.3%, n=472). With regard to STI positivity, new syphilis diagnoses were identified in 23.5% (132/560) of patients. Gonococcal and chlamydial infections were confirmed by nucleic acid amplification testing in 14.6% (82/560) and 13.4 % (75/560) of patients respectively. Three new HIV diagnoses were identified. Same-day PrEP was initiated in 16.1% (90/560) of patients, of which 56.7% were cis-female. All new PrEP starts had a follow-up appointment scheduled but only 20% (18/90) and 11.1% (10/90) of patients continued to take PrEP at 3 and 6 months respectively.
**Conclusion:** We demonstrated the feasibility of a unique workflow bringing patients from the ED to a specialized sexual health clinic. The SWC afforded the opportunity to identify and engage candidates for PrEP in a nontraditional setting, notably this included a large number of cisgender women. However, further work is needed to support the ongoing PrEP cascade. Identifying these new populations with untreated STIs and other HIV risk factors for targeted, innovative PrEP intervention is integral to local and national HIV elimination efforts.

**Table: Characteristics of Adults with Discordant Syphilis Antibody Profile from January 1 through June 30, 2018 in Montefiore Health System**

| | PWH[1] (N= 438) | On PrEP[2] (N= 60) | No PrEP [3] (N= 462) |
|---|---|---|---|
| Age, median (range), y | 51 (20-82) | 30 (20-78) | 55 (18-92) |
| Age group, y | | | |
| 18-44 | 150 (34.2%) | 48 (80.0%) | 84 (18.2%) |
| 45-59 | 194 (44.3%) | 10 (16.7%) | 205 (44.4%) |
| ≥60 | 94 (21.5%) | 2 (3.3%) | 173 (34.4%) |
| Sex | | | |
| Female | 101 (23.1%) | 2 (3.3%) | 286 (61.9%) |
| Male | 337 (76.9%) | 58 (96.7%) | 176 (38.1%) |
| Etiology of discordant syphilis antibody profile | | | |
| Prozone | 3 (0.7%) | 0 (0.0%) | 2 (0.4%) |
| Late latent | 9 (2.1%) | 1 (1.7%) | 87 (18.8%) |
| Treated | 421 (96.1%) | 58 (96.7%) | 319 (69.0%) |
| Inadequately assessed | 5 (1.1%) | 1 (1.7%) | 54 (11.7%) |
| | | | |
| Gonorrhea or Chlamydia within 3 y | 96 (21.9%) | 17 (28.3%) | 16 (3.4%) |

1 – People with confirmed HIV
2 – People without HIV but prescribed PrEP during the study period
3 – People without HIV or with unknown HIV status but presumed without HIV and not on PrEP

## 873 DISCORDANT SYPHILIS ANTIBODY TESTING AND HIV RISK IN THE BRONX, NEW YORK

**Nisha M. Patel**[1], Uriel R. Felsen[1], Martin F. Packer[1], Mindy S. Ginsberg[1], Eric A. Meyerowitz[1]
[1]*Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA*

**Background:** While syphilis is highly associated with HIV risk, the risk with a discordant syphilis antibody profile is unknown. A discordant syphilis antibody profile often indicates remote infection and is a positive initial treponemal test with a negative nontreponemal and a positive confirmatory treponemal test. Etiologies for a discordant syphilis antibody profile include previously treated, untreated late latent, and early primary syphilis with the prozone phenomenon. We estimated the proportions attributable to the various etiologies and assessed for the presence of active HIV risk.
**Methods:** Using the Einstein-Rockefeller-CUNY Center for AIDS Research Clinical Cohort Database we identified all outpatients over age 18 with a discordant syphilis antibody profile from January-June 2018 at Montefiore Health System. We performed chart review to extract clinical and sociodemographic characteristics. Most likely etiology was classified as follows: "prozone" if lab confirmed or clinically suspected, "treated" if similar prior results or prior treatment documented, "latent" if documented by provider or treatment given, or "inadequately assessed" if not clearly addressed. Those not known to be living with HIV were considered to have active HIV risk if they were prescribed PrEP, were classified as prozone, or had gonorrhea or chlamydia (GC/CT) within 3 years.
**Results:** Among 28,274 unique patients with syphilis testing in the study period, 960 (3.4%) had a discordant syphilis antibody profile. The median

age was 52 years (range 18-92), 389 (40.5%) were female, and 438 (45.6%) were living with HIV (Table). Likely etiologies were: 5 prozone, 97 latent, 798 previously treated, and 60 inadequately assessed. Among these latter 60, 7 were misinterpreted, 21 were noted as abnormal without follow-up, and the rest had insufficient documentation. Among the 522 individuals without HIV, 77 (14.7%) had evidence of active HIV risk. Among patients without HIV, 60 were on PrEP, including 17 (28.3%) with GC/CT within 3 years. Of the 462 without HIV not on PrEP, 2 (0.4%) had early syphilis with prozone and 16 (3.7%) had GC/CT within 3 years.

**Conclusion:** While the vast majority of discordant syphilis results represented remote infection, a substantial proportion of those without HIV had active HIV risk. That 55 (10.5%) of those without HIV were inadequately assessed demonstrates the complexity of syphilis results and may have implications for provider recognition of HIV risk.

## 874 INNATE IMMUNITY PREDICTORS OF HIV RISK LINKED TO GENITAL HERPES

**Yashini Govender**[1], Charles Morrison[2], Pai Lien Chen[2], Xiaoming Gao[2], Hidemi S. Yamamoto[1], Tsungai Chipato[3], Sharon Anderson[4], Robert Barbieri[1], Robert Salata[5], Gustavo Doncel[4], Raina Fichorova[1]

*[1]Brigham and Women's Hospital, Boston, MA, USA, [2]FHI 360, Durham, NC, USA, [3]University of Zimbabwe, Harare, Zimbabwe, [4]Eastern Virginia Medical School, Norfolk, VA, USA, [5]Case Western Reserve University, Cleveland, OH, USA*

**Background:** Incident HSV-2 infection is associated with over threefold increase in risk of HIV acquisition. Understanding the underlying mechanisms is a research priority given the high global HSV-2 prevalence ranging from 39 to 83 % among women in Sub-Saharan Africa. We hypothesized that: 1) aberrant innate immunity predisposes to both HIV-1 and HSV-2, and 2) innate immunity differs between incident and established HSV-2 infection, which may explain the greater HIV acquisition risk with incident HSV-2.

**Methods:** We analyzed longitudinal samples from HIV-1 negative visits of 1019 women before and after HSV-2 acquisition. We measured cervical and serum biomarkers of inflammation and immune activation previously linked to HIV-1 risk. Protein levels were Box–Cox transformed and odds ratios for HSV-2 acquisition were calculated based on top quartile or below/above median levels for all HSV-2 negative visits. Bivariate analysis determined the likelihood of HSV-2 acquisition by biomarker levels preceding infection. Linear mixed-effects models evaluated if biomarkers differed by HSV-1 status defined as negative, incident, or established infections with an established infection cut-off starting at 6 months.

**Results:** In the cervical compartment, two biomarkers of HIV-1 risk (low SLPI and high BD-2) also predicted HSV-2 acquisition, while low IL-1β, IL-6, IL-8, MIP-3α, ICAM-1 and VEGF, alone or in combinations, indicated increased HSV-2 acquisition risk. Systemic immunity predictors of HSV-2 acquisition were high sCD14 and IL-6, with highest odds when concomitantly increased (OR=2.23, 1.49-3.35). Concomitant systemic and mucosal predictors of HSV-2 acquisition risk included: 1) serum top quartile sCD14 with cervical low SLPI, VEGF and ICAM-1, or high BD-2; 2) serum high IL-6 with cervical low VEGF and ICAM-1, SLPI, IL-1β and IL-6, and 3) serum low CRP with cervical high BD-2. Most cervical biomarkers were lower after HSV-2 acquisition compared to the HSV-2 negative visits, with incident infections associated with a larger number of suppressed cervical biomarkers and lower serum IL-6 levels compared to established infections.

**Conclusion:** Predisposing factors impacting mucosal SLPI and BD-2 balance may be contributing to higher risk of both HIV-1 and HSV-2. A combination of systemic immunoinflammatory and cervical immunosuppressed states is associated with higher odds of acquiring HSV-2. A decreased innate immunity state persisting during incident herpes infection may add to the increased HIV-1 susceptibility.

## 875 GENITAL MICROBIOME AND TENOFOVIR LEVELS IN TRANSGENDER MEN AND CISWOMEN ON ORAL PrEP

**Jill Blumenthal**[1], Mackenzie L. Cottrell[2], Sheldon Morris3, Maile Y. Karris[1], Stephen A. Rawlings[1], Leah Burke[1], Sara Gianella[1], Antoine Chaillon[3]

*[1]University of California San Diego, San Diego, CA, USA, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]University of California San Diego, La Jolla, CA, USA*

**Background:** The genital environment might affect tenofovir (TFV) concentrations in cisgender women (CGW) but it has not been evaluated in transgender men (TGM). We explored differences in cervicovaginal fluid (CVF) microbiome and TFV concentrations between TGM taking or not taking testosterone (TGMT and TGMNT) and a historical cohort of CGW taking daily oral PrEP with TDF/FTC.

**Methods:** Individuals assigned female sex at birth taking oral TDF/FTC in two prospective studies in San Diego (iTAB plus Motivational Interviewing for PrEP Adherence in Transgender Individuals and Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGiS) had CVF collected at week 24 to evaluate (i) TFV concentrations and (ii) microbiome composition by 16S sequencing (V3-V4 region). Microbiome sequencing data were processed with the QIIME2 algorithm. Microbiome type was defined based on the prevalence of Lactobacilli (i.e., dominant or not). Alpha diversity was evaluated using the R Microbiome package. Beta diversity was evaluated as a principal coordinate analysis (PCoA) for the Bray Curtis dissimilarity distances and UniFrac using Phyloseq and vegan R packages. Significance of PCoA grouping was tested by analysis of dissimilarity (ADONIS) Identification of OTUs significantly different between CGW and TGMNT versus TGMT represented as log2 fold changes ≥3 for OTUs with adjusted p-values < 0.01 were calculated in the DESeq2 package.

**Results:** A total of 32 CGW and 13 TGM (n=6 TGMNT and n=7 TGMT) had CVF specimens collected at weeks 24. Median CVF TFV concentrations trended lower (~4-6-fold) among TGMT compared to TGMNT and CGW but was not statistically significant (p=0.14). CGW had significantly greater microbiome Shannon alpha diversity (4.38; 2.27, 6.42) compared to TGMNT (1.45; 0.37,1.81) and TGMT (1.66; 0.12, 2.46) (p<0.001); conversely, CGW had greater lactobacillus dominance compared to TGM (p=0.074). Beta-diversity was also significantly different between TGMNT, TGMT and CGW groups at week 24 (adonis test, p<0.0001). DeSeq2 negative binomial test revealed a significant decrease in lactobacillus in TGMT (>3 log fold change, p value <0.01) as compared to CGW and TGMNT.

**Conclusion:** Compared to CGW, TGM have lower vaginal microbiome alpha diversity but less lactobacillus dominance, which may have implications for risk of HIV acquisition from vaginal sex that deserves further investigation. In addition, the potentially lower CVF TFV levels observed in TGMT warrant greater exploration.

Table 1: Summary Descriptive by Gender Identity and Hormone Status

| | Cisgender Women (n=32) | TGM no testosterone (n=6) | TGM on testosterone (n=7) | p-value |
|---|---|---|---|---|
| Median age (IQR) | 44 (24, 56) | 27 (22, 45) | 35 (22, 37) | 0.005 |
| Race | | | | 0.15 |
| White | 21 (66%) | 3 (50%) | 4 (57%) | |
| Black | 3 (9%) | 0 (0%) | 1 (14%) | |
| Asian | 4 (12.5%) | 0 (0%) | 0 (0%) | |
| Other | 4 (12.5%) | 3 (50%) | 2 (29%) | |
| Ethnicity | | | | 0.69 |
| Hispanic | 11 (34%) | 2 (33%) | 1 (14%) | |
| Not Hispanic | 21 (66%) | 4 (67%) | 6 (86%) | |
| Creatinine Clearance (IQR) | 125 (75.0, 231) | 134 (107, 151) | 91.0 (65.0, 115) | 0.011 |
| Median weight lbs (IQR) | 180 (108, 270) | 215 (150, 289) | 177 (150, 264) | 0.16 |
| Lactobacillus dominance | | | | 0.074 |
| Lactobacillus dominant | 22 (69%) | 2 (33%) | 2 (29%) | |
| Non-Lactobacillus dominant | 10 (31%) | 4 (67%) | 5 (71%) | |
| Shannon alpha diversity | 4.38 [2.27;6.42] | 1.45 [0.37;1.81] | 1.66 [0.12;2.46] | <0.001 |
| Median CVF TFV concentration ng/mL (IQR)[a] | 854 (116, 2385) (n=34) | 1221 (182, 5017) (n=7) | 191 (25, 1061) (n=8) | 0.14 |

[a]Values below limits of quantification were imputed at ½ the lower limit of quantification

## 876 IMPACT OF NONAVALENT ANTI-HPV VACCINATION ON ORAL PAPILLOMAVIRUS INFECTION

**Roberto Rossotti**[1], Alice Nava[1], Chiara Baiguera[1], Maria C. Moioli[1], Diana Fanti[1], Federico D'Amico[1], Elvira Inglese[1], Daniele Calzavara[2], Chiara Vismara[1], Simona Bossolasco[3], Andrea M. Tamburini[3], Massimo Cernuschi[3], Francesco Scaglione[1], Massimo Puoti[1]

*[1]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, [2]Milano Checkpoint, Milan, Italy, [3]San Raffaele Scientific Institute, Milan, Italy*

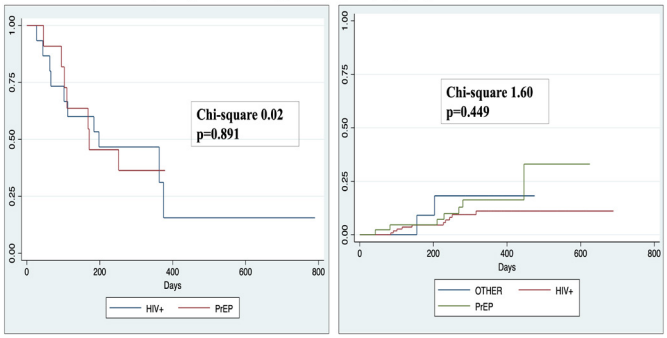
**Background:** HPV infection is the main risk factor for the development of oral, genital and anal carcinomas. Most HPV infections clear within few months while some others become persistent leading to premalignant or malignant disease. HIV infection is an additive risk factor for progression to cancer. HPV vaccination is a preventive strategy that could shorten persistent infection duration. Aim of this study is to evaluate the impact of nonavalent vaccine on oral HPV infection in a cohort of MSM and TGW.

**Methods:** This multicentric, prospective study included all MSM and TGW who started nonavalent HPV vaccination from May 2019 to May 2021. Oral rinse was collected before each vaccine administration (T0, T1, T2) and six months after the third dose (T3). Cellular pellet was extracted through an automated easymag platform and analyzed with reverse in situ ibridisation. Descriptive statistics (median and interquartile range for continuous variables, absolute and relative values for categorical variables) were used. Kaplan Meier probability curves and Cox regression models for HPV acquisition and clearance were calculated.

**Results:** The analysis included 211 individuals: 202 MSM and 9 TGW with a median age of 42 (IQR 35-50) years. The majority was HIV-infected (65%) with a good immunologic status (mean CD4 count 788 cell/mmc, IQR 600-1,047). A previous episode of anal condylomas was registered in 25% of cases. Oral rinse was already positive at baseline in 30 subjects (14%). Positivity rate did not change over time: 12% at T1, 13% at T2, and 9% at T3 (p=0.596), even when restricting the analysis only to high-risk genotypes (p=0.574) and to genotypes covered by vaccine (p=0.930). Subjects did not change their sexual behavior as suggested by a stable presence of concomitant sexually transmitted infections (36% at T0, 29% at T2, and 34% at T3, p=0.322). Figure shows Kaplan Meier curves for viral clearance and acquisition: HIV-positive individuals did not display a different trend. Cox regression models failed to identify factors associated to viral clearance while found that recreational drugs use was the only factor associated to HPV acquisition (aHR 3.52, 95% CI 1.22-10.10, p=0.019).

**Conclusion:** In this study nonavalent anti-HPV vaccination had no impact on overall oral infection. No specific HIV-related factor was associated to viral clearance or acquisition. Our data suggest that careful clinical monitoring should continue even after full nonavalent vaccination course.

**Figure.** Kaplan Meier probability curves for HPV oral clearance (left) and acquisition (right).




## 877 A RISK SCORE TO FACILITATE TARGETED STI DIAGNOSTIC TESTING IN YOUNG KENYAN WOMEN

New Investigator Scholar

**Victor Omollo**[1], Pamela Murnane[2], Renee Heffron[3], Lara Kidoguchi[3], Zachary O. Kwena[4], Elizabeth A. Bukusi[4], Connie L. Celum[3], Craig R. Cohen[2]
*[1]Kenya Medical Research Institute, Kisumu, Kenya, [2]University of California San Francisco, San Francisco, CA, USA, [3]University of Washington, Seattle, WA, USA, [4]Kenya Medical Research Institute, Nairobi, Kenya*

**Background:** Adolescent girls and young women (AGYW) in sub-Saharan Africa, a priority population for PrEP, also experience an excess risk of sexually transmitted infections (STIs). Even though most treatable STIs are asymptomatic, syndromic management remains the standard of care in low and middle income countries due to high costs and limited availability of diagnostic testing. We derived a risk scoring tool to identify AGYW at increased risk for Chlamydia trachomatis (CT) or Neisseria gonorrhoeae (GC) infection to inform targeted diagnostic testing and treatment.

**Methods:** Data are from the POWER cohort, a PrEP implementation science project for AGYW age 16-25 years at two family planning clinics in Kisumu, Kenya between 08/2017-03/2020. All women had nucleic acid amplification test (NAAT) for CT and GC at baseline and when they self-reported genital symptoms. We used the least absolute shrinkage and selection operator (LASSO) multivariable logistic regression models to derive a risk score. Coefficients in the final model were multiplied by 10 and rounded to assign points that could be easily calculated on paper in a busy clinical setting. We evaluated the area under the receiver operating curve [AUC], and estimated sensitivity and specificity at various risk score thresholds. We compared the risk score to using symptoms alone, the current approach for syndromic STI management in Africa.

**Results:** Among 996 women with CT/GC test results, 12% presented with STI symptoms, and the prevalence of CT was 17%, GC was 6%, and 21% had either. The best fit model included parameters for age, marital status, living situation, breastfeeding status, and use of family planning methods. The AUC was 0.71. A risk score >4 (52% of AGYW scored ≥4), had 78% sensitivity and 57% specificity for detection of CT or GC infection. For syndromic STI management, symptoms had 15% sensitivity and 88% specificity for GC or CT infections, thus missing 85% of all infections.

**Conclusion:** Among Kenyan AGYW in a PrEP implementation project with 21% prevalence of CT or GC, a risk scoring tool was superior to syndromic management in infection detection. The risk prediction tool would have detected 78% of infections through NAAT testing of half of the population, in contrast to 85% of the infections being missed by syndromic management. This score should be validated in other African AGYW as a promising tool to facilitate targeted STI testing to decrease CT/GC infection and its sequelae.

## 878 BACTERIAL VAGINOSIS PRIOR TO AND DURING FIRST PREGNANCY IN KENYAN AGYW AT RISK OF HIV

**Lynda M. Oluoch**[1], Alison C. Roxby[2], Nelly R. Mugo[1], Kenneth Ngure[3], Kenneth Tapia[2], Bhavna Chohan[2], Catherine Kiptinness[1], Anna Wald[2], Stacy Selke[2], Melody Wang[2], Murugi Micheni[1], Stephen Gakuo[1], Edith Kimani[1], Linet Makena[1]
*[1]Kenya Medical Research Institute, Nairobi, Kenya, [2]University of Washington, Seattle, WA, USA, [3]Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya*

**Background:** Adolescent girls and young women (AGYW) are at a high risk of HIV, STI and pregnancy soon after becoming sexually active. Hormonal shifts appear to influence vaginal dysbiosis; pregnancy at a younger age might disproportionately affect the vaginal environment to increase risk of HIV. We examined longitudinally how vaginal dysbiosis in sexually active young changes at the time of a first early pregnancy.

**Methods:** We conducted a secondary data analysis of the Girls' Health Study (GHS) program data from 2014 to 2020. Nugent scoring system was used to diagnose BV. A score of 7 and above was considered positive for BV. Poisson regression models were used to analyze longitudinal trends in BV over time, and to examine whether there is increased risk of BV at visits during pregnancy compared to visits before pregnancy. Relevant covariates were adjusted for, including socioeconomic status, marital status, sexual history and reproductive history. Time-to-event analysis was used to describe timing of pregnancy.

**Results:** We enrolled 400 AGYW, aged 16-20 years, median age 18.6 years (17.6-19.4) into the study, and followed them up for a median of 51 months (IQR: 27-57). At the end of follow-up, 306 (76%) had reported first penile-vaginal sex; median age of first sex was 18.9 years (Interquartile range (IQR): 18.3 - 19.9). Forty-two percent (127/306) of sexually active AGYW had a positive pregnancy test at least once during follow up. The percentage of participants with BV before pregnancy was 38% (45/119) and during pregnancy 23% (24/105). The adjusted relative risk (aRR) of BV during pregnancy among this cohort of AGYW was 0.66 (95% CI: 0.48, 0.92; p value= 0.015). Factors that were associated with BV during pregnancy included history of CT infection (RR:4.13; 95%CI: 1.73-9.90; p value=0.001).

**Conclusion:** Among AGYW, pregnancy was associated with a near 40% reduction in BV diagnosis. Hormonal changes in pregnancy may lead to reduction in vaginal dysbiosis. Further research to clarify mechanisms to explain this reduced risk is needed and may have implications for HIV prevention.

Table 3: Relative Risk of bacterial vaginosis (BV) among adolescent girls and young women (AGYW) (N=127) prior to pregnancy.

| Positive BV diagnosis | RR | P value | 95% Confidence Interval |
|---|---|---|---|
| Condomless sex in past 90 days | 1.5 | 0.564 | 0.38-6.00 |
| No regular source of income | 1.02 | 0.968 | 0.32-3.31 |
| Menarche to sexual debut < 3 years | 0.91 | 0.902 | 0.20-4.02 |
| Urban Residence | 2.48 | 0.067 | 0.94-6.56 |
| History of CT | 4.28 | 0.006 | 1.52-12.1 |
| History of HSV-2 | 4.12 | 0.048 | 1.01-16.77 |
| History of vaginal washing> 75% of visits | 0.66 | 0.623 | 0.12-3.44 |

*BV, bacterial vaginosis; RR, relative risk; CT, Chlamydia trachomatis; HSV-2, herpes simplex virus type 2.*
*Logistic regression using Generalized Estimating Equations was created to analyze longitudinal trends in BV prior to pregnancy. Model included condom use, income, time from menarche to first sex, residence, history of CT, history of HSV-2) and frequent vaginal washing.*

Table 4: Relative Risk of bacterial vaginosis (BV) among adolescent girls and young women (AGYW) during pregnancy, over 5 years.

| Positive BV diagnosis | RR | P value | 95% Confidence Interval |
|---|---|---|---|
| Condomless sex in past 90 days | 1.26 | 0.767 | 0.28-5.74 |
| Menarche to sexual debut <3 years | 2.5 | 0.104 | 0.82-7.82 |
| History of CT | 4.13 | 0.001 | 1.73-9.90 |
| History of HSV-2 | 1.72 | 0.403 | 0.48-6.12 |
| History of vaginal washing>75% of visits | 0.63 | 0.494 | 0.17-2.34 |

*BV, bacterial vaginosis; RR, relative risk; CT, Chlamydia trachomatis; HSV-2, herpes simplex virus type 2Logistic regression using Generalized Estimating Equations was created to analyze longitudinal trends in BV during pregnancy. Model included condom use, time from menarche to first sex, history of CT, history of HSV-2) and frequent vaginal washing.*

## 879 HIV-ASSOCIATED IMMUNE BIOMARKERS IN WOMEN AND GIRLS FOLLOWING SEXUAL VIOLENCE

**Eleanor Capozzi**[1], Katherine M. Anderson[2], Brittany A. Wood[2], Fernando Cabezas Mejia[1], Maile Y. Karris[2], Alexandra Fernandez-Desoto[2], Mimi Ghosh[1], Jamila K. Stockman[2]
*[1]George Washington University, Washington, DC, USA, [2]University of California San Diego, La Jolla, CA, USA*

**Background:** Individuals exposed to sexual violence are at increased behavioral risk for HIV and experience altered immune and stress response functioning. Yet, immuno-biological mechanisms linking sexual violence and increased HIV susceptibility are incompletely understood, especially in adolescent girls who are disproportionately affected. We aimed to evaluate genital immune dysregulation in adolescent and adult survivors of sexual violence victimization to develop inform and optimize trauma informed care.
**Methods:** We conducted a prospective case–control study of 65 women aged 14–45 years, who experienced recent consensual vaginal penetration (controls; n= 27 adults and 14 adolescents) or forced vaginal penetration in the past 30 days (cases; n=19 adults and 5 adolescents). Participants completed a survey, were tested for HIV/sexually transmitted infection and pregnancy, completed blood sampling for C-reactive protein (CRP) and adrenocorticotrophic hormone (ACTH), completed collection of cervicovaginal fluid for testing of immune biomarkers, and self-collected saliva samples for cortisol measurements. A panel of genital immune biomarkers associated with HIV acquisition and in-vitro HIV inhibition were assessed by ELISA assays. Statistical analyses were conducted by comparing biomarker values in the case and control groups, stratified by adult versus adolescent status at each visit using Wilcoxon rank-sum tests (SAS, version 9.4).
**Results:** At baseline, adolescent cases had significantly higher mean concentration of the inflammatory biomarker IL-6 (P=0.02) and significantly lower mean concentration of the anti-HIV/antimicrobial factor human beta defensin 2 (HBD-2) (p=0.04). In contrast, adult cases had marginally significant lower mean TNF-α concentrations (p=0.09) compared to controls. These changes were not observed either populations in follow-up 1 and 2. The observed changes were not explained by the presence of reproductive tract infections or menstrual cycle stage. Mean levels of ACTH and CRP were within normal clinical range and were not significantly different among the four groups.
**Conclusion:** We found indications of genital immune dysregulation following sexual violence exposure, which is distinct in adolescent girls. Our findings move forward the understanding of biologic mechanisms of HIV acquisition in sexual violence survivors. This may inform future studies on HIV prevention and trauma informed care.

## 880 INCREASED HIV TARGET CELLS IN FGT DURING FOLLICULAR PHASE OF HIV SERONEGATIVE WOMEN

New Investigator Scholar

**Sakthivel Govindaraj**[1], Tyree Staple[2], Gina Bailey Herring[2], Marisa R.Young[2], Christina Mehta[2], Alicia K. Smith[2], Lisa Haddad[3], Vijayakumar Velu[1]
*[1]Emory Vaccine Center, Atlanta, GA, USA, [2]Emory University, Atlanta, GA, USA, [3]Population Council, New York, NY, USA*

**Background: Ovarian** hormones are known to modulate the immune system in the female genital tract (FGT). We sought to define the impact of menstrual cycle phase on the mucosal microenvironment and HIV target cell availability.
**Methods:** Here, we characterized the distribution, phenotype and function of CD4 T cells with special emphasis on HIV target cells (CCR5+ and alpha4beta7+) and tissue resident memory (TRM) CD4 T cells in FGT of cycling women from endocervical cytobrush (CB) and compared with peripheral blood. We isolated cells from blood and CB of 91 healthy women and performed multi-color flow cytometry to characterize the various subsets of CD4 T cells between two study visits, timed to coincide with the luteal and follicular phases based on the participant's last menstrual period. We assessed association of cellular marker by visit, stratified by specimen type (blood and CB).
**Results:** In the blood and the FGT, mean levels of several cell types were higher in the follicular compared to the luteal phase including: CCR5 (p=0.001) and CCR5+alpha4beta7+ double positive cells (p=0.04) were higher in follicular compared to luteal phase. We also found significantly greater expression of activation markers in the FGT (HLADR, p=0.009 and CD38, p=0.007) in the CB follicular phase specimens compared to luteal phase. Similarly, we found increased expression of TRMs with significantly higher expression of CD103+ (p=0.04), CD69+(p=0.02) and CD69+CD103+ (p=0.02) in the follicular CB samples compared to luteal phase. This CD69+CD103+ population expresses significantly higher levels of HIV target cells CCR5 but not alpha4beta7 in the follicular phase (p=0.02) compared to the luteal phase. Interestingly, although there is higher activation found in the follicular phase, the regulatory T cells were significantly increased in the follicular phase (Fox-P3: p<0.0001).
**Conclusion:** We found evidence of enrichment of HIV target cells with higher activation and tissue resident and regulatory profile in the follicular phase, suggesting that CCR5+alpha4beta7+ TRM cells could be more susceptible to HIV infection during this phase of menstrual cycle.

INCREASED HIV TARGET CELLS IN FGT DURING FOLLICULAR PHASE OF HIV SERONEGATIVE WOMEN

| CD4 T cell subsets | CD4 T cell subsets in Blood comparing Luteal vs Follicular phase | CD4 T cell subsets in Cytobrush comparing Luteal vs Follicular phase |
|---|---|---|
| CD4+CCR5+ (Target cell) | No change | Increased (p=0.001) |
| CD4+α4β7+ (Target cell) | No change | No change |
| CD4+CCR5+α4β7+ (Target cell) | No change | Increased (p=0.04) |
| CD4+HLADR+ (Activation) | No change | Increased (p=0.009) |
| CD4+CD38+ (Activation) | Increased (p=0.01) | Increased (p=0.007) |
| CD4+CD69 (Activation/Tissue resident) | No change | Increased (p=0.02) |
| CD4+CD103 (Tissue resident) | No change | Increased (p=0.04) |
| CD4+CD69+CD103+ (Tissue resident) | No change | Increased (p=0.02) |
| CD4+Fox-P3+ (Regulatory) | No change | Increased (p<0.0001) |

## 881 HIGH LEVEL OF HIV VIRAL SUPPRESSION IN UGANDAN MEN WITH URETHRITIS AND BACTERIAL STI

**Evan Beck**[1], Oliver Laeyendecker[1], Sharada Saraf[1], Annet Onzia[2], Johan H. Melendez[3], Peter Kyambadde[4], Tza-Huei Wang[5], Ethan Gough[5], Yukari C. Manabe[3], Matthew M. Hamill[3]
*[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [2]Infectious Disease Institute, Kampala, Uganda, [3]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [4]Ministry of Health Uganda, Kampala, Uganda, [5]The Johns Hopkins University, Baltimore, MD, USA*

**Background:** Historically, control of HIV infection in young men living with HIV (LWH) has been problematic. We examined the STI/HIV burden in young men with urethral discharge syndrome (UDS) in Kampala, Uganda.
**Methods:** Between Oct 2019-Nov 2020, 250 men with UDS were enrolled at 6 urban sites. All HIV positive men (20%, 50/250) had plasma viral load testing (Abbott m2000 RealTime HIV-1); when VL>1000 copies/mL, resistance and recency testing (Asanté HIV-1 Rapid Recency Assay, Sedia Biosciences) were performed. Penile meatal swabs were retrospectively tested for gonorrhea, chlamydia, trichomoniasis, and Mycoplasma genitalium (Hologic Aptima CT/NG, TV, MG). Descriptive statistical analysis, logistic, and bivariable and multivariable regression were undertaken.
**Results:** Among the men LWH, 92% (46/50) had VL<1000; 4 were not suppressed, 1 of whom was previously undiagnosed. Among the viremic individuals, no major resistance mutations were found and none appeared recently infected. Men (median age 24[22;32]) reported sex partners/previous 2 months (median 2[1;2]), 61.6% engaged in transactional sex in the previous 6 months, and 48.4% reported alcohol use. 44.4% reported alcohol use before sex in the previous 6 months. Overall, 0.4% reported 'always' condom use, 21.8% continued condomless sex since onset of UDS symptoms. There was a high burden of active, undiagnosed STIs found in these men (see Table); of the 10% who had syphilis, 80% were previously undiagnosed. Agreement between HIV- and syphilis-POC and lab-based testing was 100% and 95% (19/20), respectively. By multivariable logistic regression, alcohol use (OR, 3.32 (95% CI:1.61, 7.11)), and condomless sexual activity since symptom onset (OR, 2.86 (95% CI:1.20, 6.84)) were significantly associated with HIV; 92% had at least one other STI.
**Conclusion:** Among men presenting with UDS, bacterial STIs were very common. 20% had HIV with a surprisingly high level of viral suppression and no evidence of resistance in those with detectable VL. Recency testing results were non-discriminatory; none appeared recently infected. Risk of future HIV acquisition is high in those not LWH. Given the high frequency of bacterial STI, alcohol use and unprotected high-risk sexual behavior in this population, men with UDS who test negative for HIV should be prioritized for PrEP. Future research, evaluating the effect of SARS-CoV-2 on the burden of STI and level of viral suppression in this population, is required.

Table. Prevalence of STIs among men attending government health clinics in Kampala, Uganda

| Total population | | |
|---|---|---|
| N=250 | # Positive | Prevalence (95% CI) |
| *Chlamydia trachomatis* | 51 | 20.5% (15.8%, 26.1%) |
| *Neisseria gonorrhoeae* | 163 | 66.3% (60.0%, 72.1%) |
| *Mycoplasma genitalium* | 29 | 12.0% (8.1%, 16.5%) |
| *Trichomonas vaginalis* | 3 | 1.9% (0.5%, 6.0%) |
| Syphilis | 25 | 10.0% (6.7%, 14.6%) |
| HIV | 50 | 20.0% (15.3, 25.6%) |
| 1 STI co-infection | 154 | 38.4% (34.9%, 44.8%) |
| ≥1 STI co-infection | 208 | 83.2% (77.9%, 87.5%) |
| ≥2 STI co-infection | 54 | 21.6% (16.8%, 27.3%) |

## 882 HIV, ASYMPTOMATIC STI, AND THE RECTAL MUCOSAL IMMUNE ENVIRONMENT AMONG YOUNG MSM

New Investigator Scholar

**Vanessa E. Van Doren**[1], S. A. Smith[1], Yi-Juan Hu[2], Gregory Tharp[2], Steven Bosinger[2], Cassie G. Ackerley[1], Phillip M. Murray[1], Rama R. Amara[2], Praveen K. Amancha[2], Robert A. Arthur[2], Henry R. Johnston[2], Colleen F. Kelley[1]
*[1]Emory Vaccine Center, Atlanta, GA, USA, [2]Emory University, Atlanta, GA, USA*

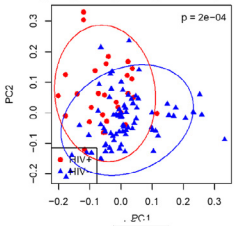
**Background:** Among young men who have sex with men (YMSM), asymptomatic rectal sexually transmitted infections (STI) such as Neisseria gonorrhoeae (GC) and Chlamydia trachomatis (CT) are common, and their potential inflammatory effects on the rectal mucosa (RM) are poorly understood.

**Methods:** YMSM living with HIV (HIV+) on ART (median CD4=635 cells/ul, viral load (VL) <20 copies/ml) and HIV-negative (HIV-) YMSM aged 18-24 years with and without asymptomatic rectal GC or CT (STI+/STI-) underwent blood and rectal biopsy collection via rigid sigmoidoscopy (n=105: 14 HIV+STI+, 15 HIV+STI-, 28 HIV-STI+, 48 HIV-STI-). We examined the RM transcriptome by RNAseq, 7 innate and 19 adaptive immune cell subsets by flow cytometry, and the microbiome by 16s rRNA sequencing. We fit linear decomposition models (LDM) to evaluate associations between HIV, STI, and cell subsets and the microbiome. Transcriptome differences were examined using DESeq2. For YMSM with and without STI, we compared median tissue HIV VL among HIV+ YMSM and median HIV p24 production in the RM explant challenge model among HIV- YMSM with non-parametric tests.

**Results:** Despite shifts in the microbiome associated with STI (LDM global p=0.04, 11 taxa detected at FDR≤0.1), there was little detectable effect of STI on the RM cellular populations, transcriptome, or HIV p24 production in rectal explants among HIV- YMSM. HIV infection alone was associated with a profound effect on RM immune cell composition (Fig 1a) but had little effect on the transcriptome or microbiome. In contrast to HIV- YMSM, there was a significant effect of STI on RM cell subsets and transcriptome among HIV+ YMSM. CD8+ IFNγ+, γδ T cells, and neutrophil populations were differentially affected among HIV+STI+ YMSM (padj<0.06). Comparing HIV+STI+ and HIV+STI- groups, we found 36 genes were upregulated (including IDO1, IL1β, FOSL1, CXCL6, and pathways involved in inflammation, cell turnover, and gut barrier function) and 7 were downregulated (FDR≤0.1, log2fold change>+/-1, Fig 1b). There was no significant difference in RM VL in HIV+ YMSM with and without STI.

**Conclusion:** Asymptomatic rectal STI is not associated with significant RM inflammation among HIV- YMSM; however, there is evidence of RM inflammation among HIV+ YMSM. Given the contribution of chronic gut inflammation to HIV morbidity and as a barrier to HIV cure, the role of asymptomatic rectal STI, particularly recurrent STI, in mediating inflammation should be further examined among HIV+ MSM.

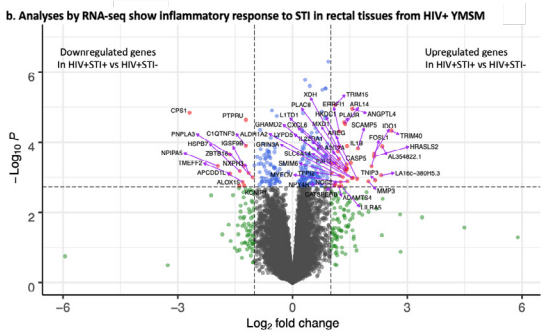
a. Analyses by flow cytometry show unique cellular composition in rectal tissues from HIV+ vs HIV- YMSM




| Rectal Mucosal Immune Cell Subsets Increased in HIV+ | $P_{adj}$ |
|---|---|
| CD8+ T cells | 0.002 |
| Memory CD8+ T cells | 0.002 |
| Ki67+ memory CD8+ T cells | 0.016 |
| Ki67+ memory CD4+ T cells | 0.04 |
| CD8+ IFNγ+ T cells | 0.002 |
| CD8+ TNFα+ T cells | 0.008 |
| CD69- CD103- CD8+ T cells | 0.002 |
| MAIT cells | 0.04 |
| Neutrophils | 0.05 |
| γδ T cells | 0.02 |

| Rectal Mucosal Immune Cell Subsets Decreased in HIV+ | $P_{adj}$ |
|---|---|
| CD4+ T cells | 0.002 |
| Memory CD4+ T cells | 0.002 |
| CCR5+ memory CD4+ T cells | 0.002 |
| CD4+ IFNγ+ T cells | 0.002 |
| CD4+ TNFα+ T cells | 0.007 |
| CD69+ CD4+ T cells | 0.03 |
| CD56+ CD16- NK cells | 0.007 |

b. Analyses by RNA-seq show inflammatory response to STI in rectal tissues from HIV+ YMSM




## 883 SYPHILIS REINFECTIONS AMONG HIV+ AND HIV- PATIENTS: A RETROSPECTIVE STUDY

New Investigator Scholar

**Giorgio Tiecco**[1], Valentina Marchese[2], Samuele Storti[1], Melania Degli Antoni[1], Silvia Amadasi[2], Maurizio Gulletta[2], Francesca Viola[2], Emanuele Focà[1], Francesco Castelli[1], Maria Eugenia Quiros-Roldan[1]
*[1]University of Brescia, Brescia, Italy, [2]Spedali Civili di Brescia, Brescia, Italy*

**Background:** Syphilis infection does not lead to definitive immunity against reinfection and crucial aspects of repeated episodes of syphilis are far from being cleared. We aimed to compare demographical, serological and clinical features of syphilis reinfections in HIV+ and HIV- patients.

**Methods:** Our Infectious Disease Unit assists 3841 HIV+ patients, with a dedicated clinic for sexually transmitted diseases which is part of the Italian Sentinel Surveillance System (SSS). We retrospectively evaluated syphilis notifications from 2013 to 2021 matching them to our electronic health record system. We considered demographical and clinical characteristics, risky habits, number of reinfections and serological response. We recorded also if a lumbar puncture (LP) was performed.

**Results:** Syphilis was diagnosed in 653 patients of whom 339 (51.9%) were HIV+ with a mean baseline CD4 count of 736 cells/uL. We recorded at least one episode of reinfection in 287 patients (44.0%): 213 (74.2%) were HIV+ with a high number of subsequent episodes per patient (range 1-12). Among HIV+ patients with syphilis reinfection, 209 (98.1%) were male, 176 (82.6%) were homo/bisexual and 181 recurrences (85.0%) were diagnosed in asymptomatic patients through annual screening. After treatment, 43 HIV+ patients (20.2%) resulted in serological-non-response (SNR) and LP was performed in 27 patients (12.7%): 6 (22.2%) asymptomatic neurosyphilis (ANS) were diagnosed. Regarding HIV- patients, the number of syphilis reinfections per patient was lower (range 1-4), females (54.1%) were more represented, 61 (82.4%) reinfections were diagnosed during latent syphilis and 7 SNR (9.5%) were recorded. LP was performed in 9 patients (12.2%) and 1 (11.1%) ANS was diagnosed.

**Conclusion:** Syphilis reinfections are predominantly diagnosed in HIV+ men who have sex with men and through periodical screening in syphilis-asymptomatic HIV+ patients, confirming that clinical manifestations in subsequent episodes of syphilis may be rare. Each additional episode of syphilis may result in a more attenuated immune response especially in HIV+ rather than HIV- patients. Considering the risks connected to a misdiagnosed ANS, an appropriate counselling to increase the acceptance of LP is crucial.

## 884 DOUBLE-DOSE ETONOGESTREL CONTRACEPTIVE IMPLANT OVERCOMES INTERACTION WITH EFAVIRENZ

**Catherine A. Chappell**[1], Mohammed Lamorde[2], Shadia Nakalema[3], Isabella Kyohairwe[3], Pauline Byakika-Kibwika[4], Leslie A. Meyn[5], Michelle Pham[6], Kimberly K. Scarsi[6]
*[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Infectious Disease Institute, Kampala, Uganda, [3]Infectious Diseases Institute, Kampala, Uganda, [4]Makerere University*

*College of Health Sciences, Kampala, Uganda, [5]Magee–Womens Research Institute, Pittsburgh, PA, USA, [6]University of Nebraska Medical Center, Omaha, NE, USA*

**Background:** Concomitant use of EFV-based ART and an etonogestrel (ENG) contraceptive implant resulted in 82% lower ENG exposure compared to women not receiving ART. We hypothesized that doubling the dose of the ENG in combination with EFV-based ART would increase ENG exposure and reduce the rate of ovulation. This study compared ENG pharmacokinetics (PK) and the rate of ovulation in women on EFV-based ART receiving two 68 mg ENG implants (DoublET) versus one 68 mg ENG implant (Control).

**Methods:** This was a randomized, open-label study of Ugandan women with HIV and regular menstrual periods on EFV 600 mg-based ART. Participants were randomized to the DoublET or Control group and the ENG implant(s) were placed in one arm at entry. A copper intrauterine device was required to prevent pregnancy. Plasma was collected at day 3 and weeks 1, 4, 12, 24, 36 and 48 after implant placement, and analyzed by a validated LC-MS/MS method for ENG. ENG concentrations were summarized as median (IQR) and compared between groups by geometric mean ratio with 90% CI. The primary endpoint was ovulation over 48 weeks; evaluated by serum progesterone concentrations over 4 consecutive weeks at months 3 (weeks 9-12), 6 (weeks 21-24) and 12 (weeks 45-48). Progesterone concentrations >3ng/mL were interpreted as consistent with ovulation. The ovulation rate in each group was compared using Fisher's exact by month and generalized estimating equations over 48 weeks.

**Results:** All participants (n=72) were cisgender Ugandan women, median age 31 (IQR 29, 36), and randomized 1:1 per group (n=36). Two participants in the Control group discontinued; one at week 1 due to undetected pregnancy at entry and another at week 45 due to mental illness. The table summarizes ENG PK results by visit. At each time point, ENG was more than two-fold higher in the DoublET group compared to controls (GMR 2.30-2.83; Table). There were 47 ovulations in 25 participants over 104 months (45%) in the Control group and 2 ovulations in 2 participants over 108 months (2%) in the DoublET group [Month 3: 11 (31%) vs 0 (0%); Month 6: 17 (49%) vs 0 (0%); Month 12: 19 (56%) vs 2 (6%), respectively (all p<0.001)]. The odds of ovulation were reduced by 97.7% (95% CI: 90.1- 99.5) in the DoublET group over 48 weeks.

**Conclusion:** For the first year of use, placing two ENG implants suppressed ovulation and increased ENG PK compared to one ENG implant among women on EFV-based ART. We recommend doubling the dose of ENG with EFV-based ART to improve contraceptive effectiveness.

**Table: Etonogestrel Plasma Concentrations Per Visit Over 48 Weeks; Median (IQR)**

| Study Visit | DoublET Group: ENG 136 mg + EFV 600 mg-based ART (pg/mL) | Control Group: ENG 68 mg + EFV 600 mg-based ART (pg/mL) | GMR (90% CI) DoublET: Control |
|---|---|---|---|
| Day 3 | 484 (306, 570) | 181 (155, 237) | 2.69 (1.83, 3.32) |
| Week 1 | 439 (327, 618) | 182 (102, 303) | 2.74 (1.68, 3.47) |
| Week 4 | 282 (158, 414) | 115 (79, 178) | 2.35 (1.54, 2.93) |
| Week 12 | 214 (124, 271) | 83 (66, 99) | 2.49 (1.56, 3.14) |
| Week 24 | 168 (91, 224) | 69 (42, 99) | 2.30 (1.48, 2.89) |
| Week 36 | 132 (75, 157) | 54 (42, 71) | 2.40 (1.50, 3.05) |
| Week 48 | 95 (69, 137) | 39 (25, 64) | 2.83, (1.89, 3.53) |

## 885 DISPARITIES IN PRENATAL SYPHILIS RISK AMONG PREGNANT WOMEN LIVING WITH HIV IN BRAZIL

**Jessica L. Castilho**[1], Fernanda F. Fonseca[2], Ahra Kim[1], Emilia M. Jalil[3], Andrea M. Beber[2], Valdilea Veloso[3], Carmen S. Domingues[2], Catherine McGowan[1], Angelica E. Miranda[2], Beatriz Grinsztejn[3], Adele S. Benzaken[2], Bryan Shepherd[1], Gerson Fernando M. Pereira[2]

*[1]Vanderbilt University, Nashville, TN, USA, [2]Ministry of Health, Brasilia, Brazil, [3]Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil*

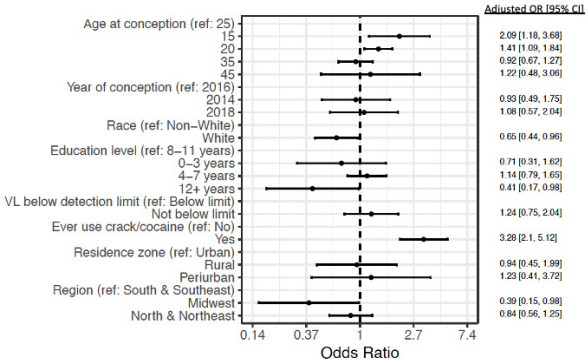
**Background:** The prevalence of prenatal syphilis, which is associated with preventable adverse pregnancy outcomes, remains high in Brazil. Little is known about the epidemiology of prenatal syphilis in pregnant women living with HIV (WLWH).

**Methods:** Retrospective data were systematically abstracted from medical records of Brazilian WLWH on ART who were pregnant between January 2015 and May 2018. Women with known pregnancy outcomes were included. Prenatal syphilis was defined as a clinical syphilis diagnosis and treatment or any positive syphilis laboratory result between 30 days before the estimated date of conception and pregnancy conclusion. Baseline characteristics and prenatal care according to prenatal syphilis status were compared using Pearson and Wilcoxon tests as appropriate. Multivariable logistic regression, with restricted cubic splines for age and multiple imputation with 20 replications to account for missing data, calculated the association of prenatal syphilis risk with sociodemographic covariates.

**Results:** Among 2015 pregnant WLWH included, 155 (7.7%) met criteria for prenatal syphilis, of whom 141 (98.6%) had documented syphilis treatment. Median gestational age at syphilis diagnosis was 14.7 weeks (IQR: 9.7-24.4). Median number of prenatal visits was seven, similar in women with and without prenatal syphilis (p=0.083). Compared to women without prenatal syphilis, those with prenatal syphilis were younger at pregnancy conception (25.8 vs. 27.6 years, p=0.020), more likely to be Black or mixed race (65.6% vs. 56.7%, p=0.031), more likely to have <8 years of education (47.3% vs. 39.6%, p=0.011), and were diagnosed with HIV in later calendar years (median year 2016 vs. 2015, p<0.001). Women with prenatal syphilis were more likely to use tobacco (25.2% vs. 10.8%), alcohol (14.8% vs. 5.4%), and crack/cocaine (12.3% vs. 2.6%) during pregnancy compared to those without syphilis (all p<0.0001). In adjusted analyses, younger age, Black/mixed race, and crack/cocaine use were strongly associated with higher odds of prenatal syphilis (Figure).

**Conclusion:** In this national cohort of pregnant WLWH in Brazil, prenatal syphilis was prevalent and increased risk of prenatal syphilis was observed among the most vulnerable WLWH. Attention to syphilis prevention, screening and treatment is especially needed in vulnerable and marginalized women.

**Multivariable logistic regression model for odds of prenatal syphilis (n=155) among 2,015 pregnant WLWH in Brazil, 2015-2018**




## 886 SCREENING OF STIs IN PREGNANCY AND PREGNANCY OUTCOMES IN WOMEN WITH AND WITHOUT HIV

New Investigator Scholar

**Dorothy C. Nyemba**[1], Remco P. Peters[2], Andrew Medina-Marino[1], Jeffrey D. Klausner[3], Phuti Ngwepe[2], Landon Myer[1], Leigh Johnson[1], Dvora Joseph Davey[1]

*[1]University of Cape Town, Cape Town, South Africa, [2]University of Pretoria, Pretoria, South Africa, [3]University of Southern California, Los Angeles, CA, USA*

**Background:** Sexually transmitted infections (STIs) in pregnancy may increase the risk of adverse pregnancy outcomes. STI syndromic management is standard of care in South Africa but has its limitations. We evaluated the impact of diagnosing and treating curable STIs in pregnancy on adverse pregnancy and birth outcomes by HIV status.

**Methods:** We combined data from two prospective studies of pregnant women attending public sector antenatal care (ANC) clinics in Tshwane District and Cape Town, South Africa. Pregnant women were enrolled and tested for C. trachomatis, T. vaginalis and N. gonorrhoeae with Xpert® using vaginal swabs. We evaluated the association between diagnosis and treatment for any STI at the first ANC visit and a composite adverse pregnancy outcome (miscarriage, stillbirth, preterm birth, early neonatal death, or low birthweight) using modified Poisson regression models, stratifying by HIV infection and adjusting for maternal characteristics.

**Results:** Among 619 women, 61% (n=380) were from Tshwane District and 39% (n=239) from Cape Town; 79% (n=486) were women living with HIV. The prevalence of any STI was 37% (n=228); C. trachomatis, 26% (n=158), T. vaginalis, 18% (n=120) and N. gonorrhoeae, 6% (n=40). Most women (94%) were given their STI tests results before leaving the clinic and all who had a positive diagnosis received treatment on the same day. There were 93% (n=574) singleton live births, 5% (n=29) miscarriages and 2% (n=16) stillbirths. Among the live births, there were 1% (n=3) neonatal deaths, 7% (n=35) low birthweight in full-term babies and 10% (n=62) preterm delivery. There were

24% (n=146) included in the composite adverse pregnancy outcome. Overall, STI diagnosis and treatment at first ANC visit was not associated with adverse outcomes in women living with HIV (adjusted relative risk (aRR); 1.43, 95% CI: 0.95-2.16) or women without HIV (aRR; 2.11, 95% CI: 0.89-5.01). However, diagnosis with C. trachomatis (aRR; 1.57, 95% CI: 1.04-2.39) and N. gonorrhoeae
**Conclusion:** Treated STIs at the first ANC visit were not associated with adverse pregnancy outcome overall. In women living with HIV, C. trachomatis or N. gonorrhoeae at first ANC were each independently associated with adverse pregnancy outcome. Our results highlight complex interactions between the timing of STI detection and treatment, HIV infection and pregnancy outcomes, and the need for continued monitoring in light of incident infections of failure to cure.

**Table 1: Association between curable STI diagnosis at 1st ANC visit and adverse pregnancy outcomes among women living with and without HIV in South Africa (2016 - 2019)**

| | All women | | Women living without HIV (n=133) | | Women living with HIV (n=486) | |
|---|---|---|---|---|---|---|
| | *Composite adverse outcome | | *Composite adverse outcome | | *Composite adverse outcome | |
| | RR (95% CI) | aRR (95% CI) | RR (95% CI) | aRR (95% CI) | RR (95% CI) | aRR (95% CI) |
| †Any STI at 1st ANC | 1.19 (0.89 - 1.59) | 1.26 (0.94 - 1.68) | 1.43 (0.66 - 3.10) | 2.11 (0.89 - 5.01) | 1.12 (0.82 - 1.52) | 1.43 (0.95 - 2.16) |
| **Any STI at 1st ANC (*C.trachomatis/N.gonorrhoeae*) | 1.15 (0.85 - 1.57) | 1.24 (0.91 - 1.68) | 1.32 (0.57 - 3.05) | 1.96 (0.72 - 5.31) | 1.10 (0.79 - 1.53) | **1.57 (1.03 - 2.38)** |
| *C. trachomatis* during pregnancy | 1.13 (0.83 - 1.55) | 1.22 (0.89 - 1.67) | 1.38 (0.60 - 3.18) | 2.01 (0.75 - 5.33) | 1.07 (0.76 - 1.50) | **1.57 (1.04 - 2.39)** |
| *T. vaginalis* during pregnancy | 1.09 (0.77 - 1.56) | 1.11 (0.78 - 1.58) | 1.27 (0.43 - 3.76) | 1.73 (0.56 - 5.26) | 1.03 (0.71 - 1.50) | 1.06 (0.65 - 1.74) |
| *N. gonorrhoeae* during pregnancy | 1.35 (0.81 - 2.26) | 1.48 (0.89 - 2.44) | 1.96 (0.37 - 10.26) | 3.58 (0.58 - 21.84) | 1.25 (0.73 - 2.15) | **1.69 (1.09 - 3.08)** |
| Coinfection of STIs at 1st ANC | 1.06 (0.69 - 1.63) | 1.17 (0.76 - 1.79) | 1.48 (0.41 - 5.28) | 2.96 (0.68 - 12.80) | 0.98 (0.62 - 1.55) | 1.45 (0.86 - 2.46) |

RR, relative risk; aRR, adjusted relative risk; STI, sexually transmitted infection; CI, confidence interval; ANC, antenatal care
Modified Poisson regression with robust error measurements was used to calculate RR and aRR adjusting for maternal age, gestational age at enrolment, employment, marital status, gravidity and CD4 count at enrolment for women living with HIV
STIs refers to *C. trachomatis, T. vaginalis* and *N. gonorrhoeae*
*Composite adverse outcome combines low birthweight< 2500g, preterm birth, miscarriage, stillbirth and early neonatal death
†Any STI at 1st ANC is the exposure of interest
**Any STI at 1st ANC excluding *T. vaginalis* is the exposure of interest

## 887 IMPROVING TIME TO VIRAL SUPPRESSION: 5 YEARS POST-IMPLEMENTATION OF RAPID ART START

**Stephen Gurley**[1], Jonathan Y. Huang[1], Sean Evans[1], Alexander Commanday[1], Melanie Strahm[2], Laura Carter-Williams[2], Katrina Barnes[2], Lisa Roland[2], Wendy S. Armstrong[1], Minh Ly T. Nguyen[1], Jonathan A. Colasanti[1]
*[1]Emory University, Atlanta, GA, USA, [2]Grady Health System, Atlanta, GA, USA*

**Background:** Ending the HIV Epidemic (EHE) calls for rapid treatment of HIV to achieve viral suppression (VS), as one way to curb new HIV infections. Rapid initiation of ART is now recommended by all major HIV guidelines. Rapid initiation of ART is critical in the American South, where barriers to care entry and ART initiation are disproportionately high. We describe time to VS trends in a predominately Black, un- and underinsured population of ART-naïve persons with HIV (PWH) entering care since the implementation of Rapid ART in an urban, EHE jurisdiction clinic.
**Methods:** We examined ART-naive, adult PWH new to HIV care (eg, detectable viral load at clinic entry and no self report of prior ART) at an HIV clinic in Atlanta, GA who enrolled in care between 2016-2020. We calculated time to first undetectable HIV viral load (<2.3 log-copies/$mm_3$) and frequency statistics for demographic variables by year of enrollment. Kaplan-Meier survival and Cox proportional hazards analysis were used to assess temporal trends in time to first undetectable viral load, adjusting for sex, race, and HIV risk factor.
**Results:** Among 688 ART-naive PWH enrolled in care, 77.3% were males, 85% were Black, 7% were Hispanic, 69% were aged 18-39, 54% were men who have sex with men, 41% reported current or former substance use, and there was a median annual income of $15,600. The median CD4 at enrolling was 250 cells/mL (IQR 362 cell/mL), with 53.7% <200 and 33.6% <50, and the median HIV viral load (VL) was 4.51 log-copies/mL (IQR 1.94 log-copies/mL). 74.71% of the cohort obtained an undetectable VL during follow up. The overall median time from enrollment to first undetectable viral load was 61 days (IQR: 34, 155). From 2016-17 to 2018-19, the median time from enrollment to first undetectable VL decreased by 40% from 62 days (IQR 146) to 37 days (IQR 56 days) (Kaplan-Meier Log-Rank p<0.05). Moreover, Cox hazard analysis revealed those in 2018-19 obtained a first undetectable viral load 1.399 (1.035, 1.891, p<0.05) times more quickly than those 2016-17, after adjusting for sex, race, income, and age.
**Conclusion:** Time to first VS improved over time after initial implementation of Rapid ART in this clinical setting. Improved clinical outcomes over time mirrored clinic-wide increases in funding and implementation infrastructure. While further analysis is needed to determine persistence of VS among these patients, these trends in decreasing time to initial VS indicate progress toward EHE even in one of the hardest hit regions.

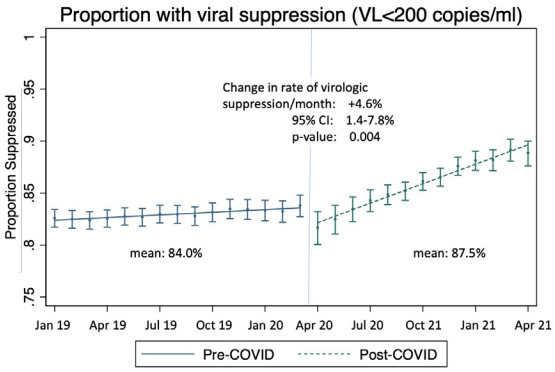
| Variable: | 2016 | 2017 | 2018 | 2019 | 2020 | Total: |
|---|---|---|---|---|---|---|
| N | 167 | 166 | 151 | 112 | 36 | 688 |
| Average Age at Enrollment, years, +/- std dev | 34.73+/-13.25 | 37.25 +/- 12.51 | 35.46 +/-12.66 | 37.55 +/- 14.6 | 32.92 +/- 11.86 | 35.9 +/-13.13 |
| Average Age at Diagnosis, years, +/- std dev | 33.75 +/- 14.28 | 35.43 +/- 12.61 | 33.86 +/- 11.76 | 35.47 +/- 14.07 | 32.49 +/- 12.57 | 34.4 +/- 13.1 |
| Natal Sex | 77.78% Male 22.22% Female | 80.46% Male 19.54% Female | 77.12% male 22.88% female | 70.69% Male; 29.31% Female | 72.22% male; 27.78% female | 76.90% Male, 23.10% Female |
| Race | 84.85% Black 4.04% White 6.57% Hispanic 4.54% Other or Multiracial | 82.76% Black 8.05% White 3.43% Hispanic 5.74% Other or Multiracial | 81.05% Black, 5.88% white, 12.42% Hispanic, 0.65% Other or Multiracial | 95.69% Black; 0.86% White; 2.56% Hispanic; 0.86% other | 80.56% Black; 5.56% White; 11.11% Hispanic, 2.78% other or multiracial | 85.23% Black 5% White 6.58% Hispanic 2.9% Other or Multiracial |
| Ethnicity | 92.93% Non-Hispanic; 7.07% Hispanic | 95.40% Non-Hispanic, 4.02% Hispanic | 87.7% Non-Hispanic, 12.34% Hispanic | 96.58% Non-Hispanic; 3.42% Hispanic | 91.67% Non-Hispanic; 8.33% Hispanic | 93.0% Non-Hispanic 6.9% Hispanic |
| Median Yearly Income, USD, (IQR) | $15,000 ($16,100) | $17,000 ($12,512) | $16,718 ($15690) | $11,740, ($20,000) | $8,010 ($18,000) | $15,600 ($17,804) |
| HIV Transmission Risk Factor | 59.60% MSM 38.89% Heterosexual 1.01% IVDU 0.51% unknown | 56.32% MSM 37.93% Heterosexual 0.57% IVDU 4.60% unknown | 53.59% MSM 44.44 Heterosexual 0.65% IVDU 1.2% unknown | 44.83% MSM 50% Heterosexual 0.86% IVDU 3.45% unknown | 38.89% MSM 52.78% Heterosexual 8.33% Unknown | 53.8 % MSM 42.4% Heterosexual 0.7% IVDU ; 2.7% unknown |
| Current or Former Substance Use | 39.9% reported current or former drug use | 44.83% report current or former drug use; 55.17% do not report | 39.87% report current or former substance use, 60.13% do not report | 43.97% report current or former subst ; 56.03% do not report | 38.89% Report current or former use; 61.11% do not | 43.36% Current or Former Substance Use 56.64% No Reported Current or Former Use |
| Median Baseline CD4, cells / mm^3 (IQR) | 195.5 (384) | 288 (348) | 226.5 (359.5) | 237 (347) | 272.5 (388) | 250 (362) |
| CD4 categories: CD4<50 CD4<200 CD4>200 | <50 45.96%; 50 to 200: 22.22%; >200: 31.82% | <50: 19.54%; 50 to 200: 22.99%; >200: 57.47% | <50: 28.10%; 50 to 200: 18.95%; >200: 52.94% | <50: 33.03%; 50 to 200: 16.38%; >200: 50% | <50: 11.11%; 50 to 200: 25.00%; >200 63.89% | <50: 33.62%; 50 to 200: 20.06% >200: 328% |
| Median Baseline VL, log copies / mm^3 (IQR) | 4.25 (2.31) | 4.605 (2.17) | 4.61 (1.65) | 4.54 (1.49) | 4.79 (2.55) | 4.53 (1.94) |
| VL Categories: VL<5 VL>5 | <5: 82.32%; >5: 17.68% | <5: 66.67%; >5: 33.33% | <5: 66.01%; >5: 33.99% | <5: 69.83%; >5: 30.17% | <5: 58.33%; >5 41.67% | <5: 72.32% >5: 27.68% |
| Achieved UVL | 81.31% UVL; 18.69% no UVL | 67.82% UVL; 32.18% no UVL | 76.47% UVL; 23.53% no UVL | 73.28% UVL; 26.86% no UVL | 75% UVL; 25% no UVL | 74.71% UVL; 25% no UVL |
| Of those UVL, how many in 6m? | 75.16% in 6m; 24.84% >6m | 69.49% in 6m; 30.51% >6m | 79.49% in 6m; 20.51% >6m | 90.59% in 6m; 9.41% >6m | 81.48% in 6m; 18.52% >6m | 77.89% UVL in 6m; 22.11% >6 |
| Of those UVL, how many in 12m? | 87.58% in 12m; 12.42% in >12m | 83.05% in 12m; 16.95% in >12m | 89.74% in 12m; 10.26% in >12m | 95.29% in 12m; 4.71% >12m | 100% in 12m. | 89.04% UVL in 12m; 10.96% >12m |
| Median Days from Enrollment to First UVL, (IQR) | 62 (146) | 95 (181) | 48 (94) | 37 (56) | 49 (107) | 61 (121) |

## 888 INCREASED HIV VIRAL SUPPRESSION DURING COVID-19 AMONG US URBAN PEOPLE WITH HIV

**Matthew A. Spinelli**[1], Noelle LeTourneau[1], Dave Glidden[1], Ling Hsu[2], Matthew D. Hickey[1], Elizabeth Imbert[1], Mireya Arreguin[1], Jennifer Jain[1], Jon J. Oskarsson[1], Susan P. Buchbinder[2], Mallory Johnson[1], Diane V. Havlir[1], Katerina Christopoulos[1], Monica Gandhi[1]
*[1]University of California San Francisco, San Francisco, CA, USA, [2]San Francisco Department of Public Health, San Francisco, CA, USA*

**Background:** After COVID-19 shelter-in-place (SIP) orders on 3/16/2020, viral suppression (VS) rates initially decreased within a safety-net HIV clinic in San Francisco, with greater decreases among homeless people living with HIV (PLWH). We sought to understand if (1) proactive outreach to provide social services, (2) scaling up of in-person visits for most patients and drop-in visits at the clinic, and (3) expansion of housing programs could reverse this decline.
**Methods:** We assessed VS 24 months before and 13 months after SIP using mixed-effects logistic regression and propensity score methods, followed by interrupted time series (ITS) analysis to examine changes in the rate of viral suppression per month. Loss to follow-up was assessed via active clinic outreach and tracing using Kaplan-Meier methods.
**Results:** The cohort contained 1816 patients with a median age of 51; 12% female, 14% unstably housed, and 15% with CD4+-cell counts <200 cells/$mm_3$. The adjusted odds of VS increased 1.34-fold following the intervention (95% CI: 1.21-1.46), with similar results using inverse probability weighting (adjusted odds ratio (AOR) 1.31; 95% CI: 1.17-1.46). Results from the ITS analysis show that the odds of VS continuously increased by 1.05-fold per month over the post-intervention period (95% CI: 1.01-1.08, Figure). Proactive phone outreach successfully reached 90.0% of the clinic to offer services. The one-year cumulative loss to follow-up rate was 3.2% (95% CI: 2.5-3.9%). The proportion of total attended visits that were telephone visits decreased from a maximum of 64.9% to a minimum of 10.1% at the end of the analysis period. The rate of viral load monitoring decreased by 15% after the institution of SIP (95% CI: 0.83-0.88). Among homeless PLWH, the AOR for VS was 1.70 (95% CI: 1.24-2.34) and there was a 5.9% increase in VS per month using ITS methods (95% CI: 1.0-12.3%).
**Conclusion:** After an initial destabilization in VS in a large safety-net clinic following SIP orders, the VS rate increased following scale-up of in-person visits, clinic outreach to patients, intensification of social services during this time, and access to COVID-related housing programs. The loss to follow-up rate was similar or lower compared to prior years. Maintaining in-person care for

underserved patients, with flexible telemedicine options, along with provision of social services and permanent expansion of housing assistance programs, will be needed to support VS among underserved populations during the COVID-19 pandemic.




## 889 WITHDRAWN

## 890 LINKAGE TO CARE AND TIME TO VIRAL SUPPRESSION IN PWH IN SPAIN: 2004-2020

**Belen Alejos**[1], Cristina Díez[2], Maria José Galindo[3], Juan C. Lopez[2], Victoria Hernando[1], Oskar Ayerdi[4], Maria M. Alonso[5], Vicente Estrada[6], Juan A. Pineda[7], Alvaro Mena[8], María Novella Mena[9], David Dalmau[10], Inma Jarrín[1], Juan Berenguer[2]

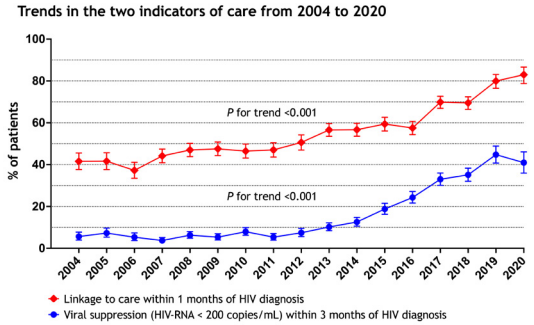
*[1]Institute de Salud Carlos III, Majadahonda, Spain, [2]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [3]Hospital Universitario y Politecnico La Fe, Valencia, Spain, [4]Centro Sandoval, Madrid, Spain, [5]Hospital Universitario de Canarias, San Cristóbal de La Laguna, Spain, [6]Hospital Universitario Clínico San Carlos, Madrid, Spain, [7]Hospital Universitario de Valme, Seville, Spain, [8]University Hospital of La Coruña, La Coruña, Spain, [9]Hospital Universitario Príncipe de Asturias, Madrid, Spain, [10]Hospital Universitari Mútua de Terrassa, Terrassa, Spain*

**Background:** For newly diagnosed persons with HIV (PWH), early initiation of ART is essential in reducing morbidity and mortality and decreasing the risk of transmitting HIV. We have previously reported the trends in linkage to HIV medical care within one month of HIV diagnosis (LC-1Mo) and viral suppression within three months of HIV diagnosis (VS-3Mo) among PWH in Spain from 2004 to 2018. We herein update this information up to 2020.

**Methods:** Longitudinal study based on the Cohort of the Spanish AIDS Research Network (CoRIS). VS was defined as ever having an HIV-RNA <200 copies/mL. We used logistic regression to assess differences by sex, age, country of birth, transmission category, and baseline CD4+ cell count.

**Results:** A total of 13,632 PWH were enrolled in CoRIS in the study period: males 85%, men having sex with men (MSM) 62%, median age 35 (IQR: 28-43) years. LC-1Mo increased from 41% (95% CI, 37% – 45%) in 2004 to 83% (79% –87%) in 2020 (P trend <0.001) (Figure). Median CD4+ cell counts at ART initiation increased from < 250/$mm_3$ in 2004-2005 to > 350/$mm_3$ since 2012 (P for trend <0.001). The percentage of initial ART regimens based on integrase strand transfer inhibitors (InSTI) increased from 3% in 2004 to > 70% from 2016 onwards (P trend <0.001). VS-3Mo increased from 6% (4% – 8%) in 2004 to 43% (40% – 47%) in 2019 with a small decrease to 41% (36%–46%) in 2020 (P trend [for the entire period] <0.001) (Figure). The odds of achieving VS-3Mo was higher among females (aOR, 95% CI: 1.30, 1.12-1.51), among non-Spanish Europeans and Latin Americans compared to native-born Spaniards (1.26, 1.11-1.44 and 1.36, 1.21-1.52, respectively), and among those older than 50 years (1.20, 1.03-1.41). Opposite, the odds of achieving VS-3Mo was lower among IDU compared to MSM (0.53, 0.40-0.70) and those with CD4 counts between 200-500 cells/uL (0.78, 0.69-0.89) and CD4 counts >500 cells/uL (0.51, 0.44-0.60) compared to those with CD4 < 200 cells/uL.

**Conclusion:** Indicators of care have improved among newly diagnosed PWH in Spain over the last 16 years. Elimination of CD4 cell count restrictions for ART initiation and increasing use of InSTI-based regimens was decisive for progress. A slight decrease in VS-3Mo in 2020 compared with 2019 was observed, perhaps because of the COVID-19 pandemic.



## 891 RCT OF A MULTISECTORAL AGRICULTURAL INTERVENTION TO IMPROVE HIV AND HEALTH OUTCOMES

**Craig R. Cohen**[1], Elly Weke[2], Edward A. Frongillo[3], Lila A. Sheira[1], Rachel L. Burger[1], Adrienne R. Mocello[1], Pauline Wekesa[4], Shari Dworkin[5], Kate Scow[6], Harsha Thirumurthy[7], Starley R. Shade[1], Lisa Butler[8], Elizabeth A. Bukusi[4], Sheri D. Weiser[1]

*[1]University of California San Francisco, San Francisco, CA, USA, [2]Kenya Medical Research Institute, Kisumu, Kenya, [3]University of South Carolina at Columbia, Columbia, SC, USA, [4]Kenya Medical Research Institute, Nairobi, Kenya, [5]University of Washington Bothell, Bothell, WA, USA, [6]University of California Davis, Davis, CA, USA, [7]University of Pennsylvania, Philadelphia, PA, USA, [8]University of Connecticut, Storrs, CT, USA*

**Background:** Food insecurity and HIV viral suppression are linked through nutritional, mental health, and behavioral pathways. We examined the effects of a multisectoral agricultural intervention on HIV viral suppression, nutritional status, and mental health among people living with HIV (PLHIV) taking antiretroviral therapy (ART) in Kenya.

**Methods:** For the Shamba Maisha cluster RCT (NCT02815579) we randomly allocated 16 health facilities (1:1; match-paired) in Kenya to intervention or control arms. The intervention included a bank loan to purchase farming commodities including a human-powered irrigation pump, fertilizer and seeds plus training in sustainable agriculture and financial literacy. Participants were ≥18 years old, on ART >6 months, moderately-to-severely food insecure, with access to farmland and water. Every 6 months participants were followed for 24 months. The primary outcome was change from baseline to endline in viral suppression (<200 copies/mL), compared between arms using difference-in-differences analyses. Secondary outcomes included changes in food insecurity, ART adherence, clinic attendance, depression, self-confidence, and social support.

**Results:** Between June 2016 and December 2017, we enrolled 366 and 354 participants in the intervention and control arms, respectively. Fifty five percent of participants were women. Retention at 24 months was 94.0%. HIV viral suppression increased in both arms from baseline to endline: intervention 85.8% to 95.1% and control 82.4% to 94.3% (p=0.86). The proportion of participants who missed a scheduled HIV clinic visit as well as adherence to ART were not different by arm. Levels of food insecurity decreased more in the intervention than control arm. The proportions of those with depression declined more in the intervention arm. Self-confidence and social support both improved more in the intervention arm (see Table).

**Conclusion:** A multisectoral agricultural intervention reduced food insecurity and depressive symptoms, and improved self-confidence and social support among PLHIV. Because viral suppression approached the UNAIDS goal of ≥95% among all participants, who resided in settings with widespread test and treat policies, no additional effects of the intervention on HIV clinical indicators occurred. Interventions that improve livelihoods may help address the structural drivers of poor health and co-morbidities affecting PLHIV in resource limited settings.

| Table | Control (n = 354) | | Intervention (n = 366) | | Trend per 24 months | | Difference in trend between arms | 95% CI | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 24-Months | Baseline | 24-Months | Control | Intervention | | | |
| | N (%) or Median (IQR) | | N (%) or Median (IQR) | | | | | | |
| **HIV Outcomes** | | | | | | | | | |
| Had undetectable viral load (<200 copies/mL) | 291 (82.4) | 314 (94.3) | 314 (85.8) | 327 (95.1) | 1.65 | 1.57 | -0.08* | (-1.0, 0.84) | 0.86 |
| **Food Insecurity** | | | | | | | | | |
| Food Insecurity Score (0-27, higher=more insecure) | 20.0 (17.0, 24.0) | 15.0 (14.0, 19.0) | 22.0 (20.0, 25.0) | 14.0 (11.0, 18.0) | -4.51 | -8.05 | -3.54 | (-4.16, -2.92) | < 0.001 |
| **Nutrition** | | | | | | | | | |
| Body Mass Index (kg/m2, continuous) | 21.5 (19.7, 23.7) | 21.8 (19.0, 24.5) | 21.5 (20.0, 23.8) | 22.1 (20.2, 24.6) | 0.57 | 0.36 | -0.21 | (-0.39, -0.04) | 0.02 |
| **Behavioral Pathway** | | | | | | | | | |
| Missed scheduled HIV visit in the past 6 months | 107 (30.3) | 20 (6.0) | 141 (38.6) | 60 (17.5) | -0.352 | -0.326 | 0.03 | (-0.08, 0.13) | 0.64 |
| ART Adherence (continuous, self-report) | 100 (98.3, 100) | 100 (100, 100) | 100 (98.3, 100) | 100 (100, 100) | 0.54 | 0.55 | 0.01 | (-0.82, 0.84) | 0.98 |
| **Mental Health** | | | | | | | | | |
| Had probable depression | 106 (29.9) | 41 (12.3) | 169 (46.3) | 36 (10.5) | -1.97 | -2.80 | -0.83 | (-1.45, -0.20) | 0.001 |
| Social Support Score | 18.0 (14.0, 21.0) | 18.0 (13.0, 21.0) | 17.0 (14.0, 21.0) | 13.0 (11.0, 16.0) | -0.50 | -4.13 | -3.63 | (-4.30, -2.95) | <0.001 |
| **Empowerment** | | | | | | | | | |
| Self-Confidence Score (0-10, lower = more confident) | 5.0 (4.0, 6.0) | 4.0 (4.0, 6.0) | 5.0 (4.0, 7.0) | 4.0 (4.0, 6.0) | -0.37 | -0.74 | -0.37 | (-0.59, -0.15) | 0.001 |

* Difference-in-differences estimates for detectable viral load calculated between visit 1 and visit 5 (~24 months)

## 892 VIRAL LOAD MONITORING IN PUBLIC SECTOR CLINICS IN RURAL SOUTH AFRICA

**Collins Iwuji**[1], Lusanda Mazibuko[2], Meg Osler[3], Tshwaraganang Modise[2], Dickman Gareta[2], Siphephelo Dlamini[2], Patrick Gabela[4], Nompumelelo Khoza[4], Thabani Mtshali[4], Mark Siedner[4], Kathy Baisley[4], Andrew Boulle[3], Kobus Herbst[4]

*[1]University of Sussex, Brighton, UK, [2]Africa Centre for Population Health, Mtubatuba, South Africa, [3]University of Cape Town, Cape Town, South Africa, [4]Africa Health Research Institute, Mtubatuba, South Africa*

**Background:** Data from the public antiretroviral treatment (ART) register (TIER.Net) showed only a third of patients starting ART had viral load measured after 12 months. It is unclear how information from TIER.Net correlates with the true viral load monitoring (VLM) that patients receive and performance of the ART programme. We examined the clinical records of HIV-positive individuals aged ≥16 years from public sector ART clinics in rural Hlabisa and compared with records in TIER.Ne

**Methods:** We selected a random sample of individuals from 10 public sector clinics who started ART in 2018 and were still in care on 28 February 2020. Sampling was proportional to the size of the HIV-positive cohort on ART in each clinic. We calculated the proportion of patients with i) VL results documented in clinic charts 12 months (± 3 months) after starting ART; ii) VL <50 c/mL according to charts; ii) VL <50 c/mL according to TIER.Net; iv) missing clinical charts; v) missing charts but VL captured in TIER.Net.

**Results:** Of 800 clinic charts selected for review, 69.4% were female and median age was 32.5 years (IQR 25-39). Based on clinic charts, 285 (35.6%) individuals had VLM at 12 months (range across the 10 clinics 14.3%-76.7%). Among those, 214/285 (75.1%) had VL<50 copies/mL (range 52.6%-93.3%). 466/800 (58.3%) had VLM at 12 months documented in TIER.Net, and 251/800 (31.4%) were captured both in TIER.Net and clinic charts. Charts were missing for 190 (23.7%) individuals (range 2.2%-44.1%); the proportion with missing charts increased with clinic size. Of those with missing charts, 152 (80.0%) had VL documented in TIER.Net.

**Conclusion:** This study confirms earlier analyses suggesting suboptimal VLM in public sector clinics in rural South Africa. In about a quarter of cases, clinicians will have no information about a patient's prior care due to missing records. There is an urgent need to improve VLM to enable early detection and prompt management of virological failure in order to achieve UNAIDS 95-95-95 targets by 2030.

## 893 INNOVATION TO ACHIEVE THE SECOND 95 AMIDST COVID-19 IN KEY POPULATION IN NIGERIA

**Bolanle Oyeledun**[1], Obioma Azurunwa[1], Christian Onyia[1], Collins Imarhiagbe[1], Francis Ogirima[1], Ezinne Akinola[1], Pius Izere-Christopher[1], Inyang Ayo[1], Evelyn Urueye[1], Emeka Kanebi[1]

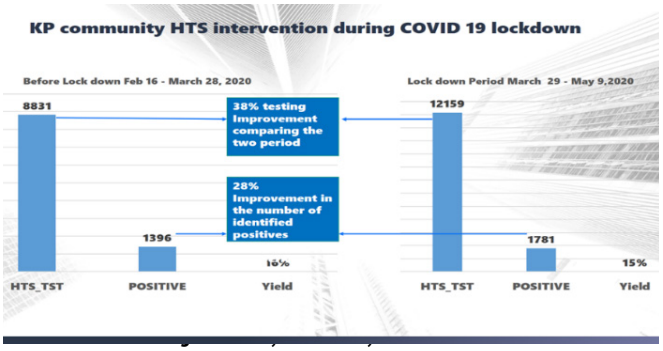
*[1]Centre for Integrated Health Programs, Abuja, Nigeria*

**Background:** Key Populations (KP) makeup 3.4% of the general population, yet account for ~32% of new HIV infections in Nigeria (NACA, 2017). With criminalizing laws, and ~3000 active KPs hotspots in Lagos state alone, it is increasingly challenging for civil society organizations to reach these groups with the much needed HIV services. With the COVID-19 outbreak in the South-West region of Nigeria, Lagos state in early March, 2020 and attendant lockdown leading to restriction in movement, it became even more challenging to reach KP members with a complement of comprehensive HIV services. We describe our experience implementing innovatively evidence and community-based strategies to scale active HIV case-finding using a COVID-19 guided protocol during the 6-week lockdown in the state.

**Methods:** We set up 22 Community ART (cART) teams split into an 8-person KP peer-led sub team comprising (community health worker, pharmacist, laboratory technician, four counselor testers, and a community mobilizer) that conducted HIV Testing Services (HTS) in 78 communities across 7 districts using the "moonlight testing" (nightly testing) approach. The teams were equipped with a line-list of index clients for elicitation of sexual and needle-sharing partners. Community engagement of gate keepers of pre-mapped KP communities was innovatively conducted, to seek approval, grant access and provide security during testing of elicited partners. Following an orientation on COVID-19 protocols for clients assessing services, index partners who accepted HTS were provided HIV prevention information, condom messaging, demonstration and distribution; those who tested positive were retested and provided with ART immediately.

**Results:** Prior to the lockdown (February –March 2020), 8,831 clients were offered HIV testing services with 1,396 (positivity yield of 16%). Following the lockdown period which lasted for 6 weeks (March- May, 2020), HIV testing among key population increased by 38% (12, 159) with a 28% increase (1, 781) in HIV positives and 15% positivity yield.

**Conclusion:** Despite the pre-existing challenges with KP access to comprehensive differentiated services worsened by current COVID-19 realities, peer-led cART showed significant promise in accelerating KP HIV case finding and sustaining community ART delivery.




## 894 GENERIC DARUNAVIR AND DOLUTEGRAVIR ARE COST-EFFECTIVE IN SECOND-LINE ART

**Jennifer Campbell**[1], Janne Estill[2], Zachary Panos[1], Joseph Harwell[1], Marta Prescott[1], Paul Domanico[1], Carolyn Amole[1]
[1]*Clinton Health Access Initiative, Boston, MA, USA,* [2]*Estill Epidemiology Consulting, Tallinn, Estonia*

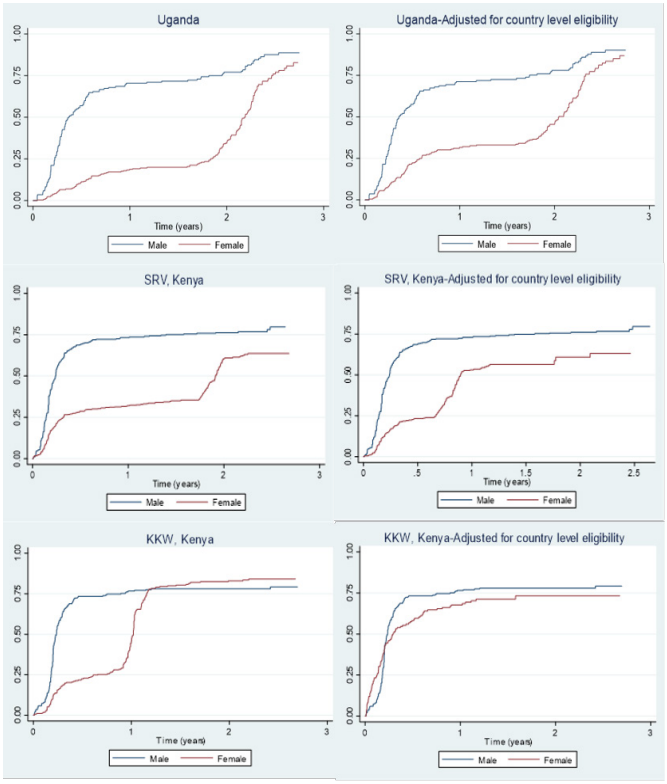
**Background:** There will be greater need for second-line (2L) antiretroviral treatment (ART) as HIV treatment programs mature. Historically, most 2L regimens in resource-limited settings contained a ritonavir-boosted protease inhibitor (PI), either lopinavir (LPV/r) or atazanavir (ATV/r). The best-in-class PI, ritonavir-boosted darunavir (DRV/r), is now available as a generic with a lower cost than LPV/r. This, together with use of dolutegravir (DTG) in 2L, offer opportunities to optimize 2L regimens.
**Methods:** We used the Applied Cost and Outcomes Research Analysis (ACORA) Model, coded in R, to compare the cost-effectiveness of 2L ART strategies. Markov state transitions were used to simulate an open patient cohort on ART through health states of ART on treatment status, viral load, CD4 cell count, and opportunistic infections (OI). We conducted a 10-year forecast using quarterly time-steps. Disability weights were applied to health states and adverse events (AEs) to estimate quality adjusted life years (QALYs). We included the costs of drugs, lab monitoring, human resources, and OI management. Disease progression was parameterized and drug profiles estimated using published literature and programmatic sources, standardized to account for multiple studies. Transitions were driven by drug-specific profiles of failure rates and discontinuations due to AEs, which were estimated from published clinical trials and standardized to account for multiple studies. We defined 4 scenarios: 1) Standard of Care (SOC): uses ATV/r and LPV/r in 2L; 2) C1: switches LPV/r to DRV/r; 3) C2: switches both ATV/r and LPV/r to DRV/r; and 4) C3: switches LPV/r and ATV/r to DTG, reserving DRV/r for those with 1L DTG failure. The analysis considered a hypothetical sub-Saharan African country with 1,000,000 existing ART patients and 100,000 new patients initiating ART each year; the SOC was either 80% LPV/r and 20% ATV/r, or the opposite. Costs and QALYs are restricted to patients who migrate to 2L. Incremental cost effectiveness ratios (ICER) are presented.
**Results:** Strategy C3 was cost-saving and maximized QALYs in both LPV/r- and ATV/r-dominant scenarios (Table). Strategies C1 and C2 resulted in higher costs and QALYs than SOC, with ICERs ranging from $34 to $1688.
**Conclusion:** In most settings It is highly cost-effective to replace LPV/r and ATV/r with DRV/r with a less than 1x GDP threshold. The most optimal strategy is to maximize use of DTG in 2L, which was the most effective and cheapest scenario across all comparisons.

| | Scenario | Total Cost (USD million) | Total QALYs (thousands) | ICER compared with SOC (A$/ΔQALY) |
|---|---|---|---|---|
| Lopinavir dominant | SOC | $ 416 | 974 | |
| | C1 – DRV/r for LPV/r | $ 417 | 1,006 | $ 34 |
| | C2 – DRV/r for LPV/r and ATV/r | $ 432 | 1,013 | $ 411 |
| | C3 - DTG in 2L (DRV/r if DTG in 1L) | $ 333 | 1,019 | cost-saving |
| Atazanavir dominant | SOC | $ 368 | 976 | |
| | C1 – DRV/r for LPV/r | $ 372 | 983 | $ 481 |
| | C2 – DRV/r for LPV/r and ATV/r | $ 432 | 1,013 | $ 1,688 |
| | C3 - DTG in 2L (DRV/r if DTG in 1L) | $ 333 | 1,019 | cost-saving |

## 895 TRANSITIONING WOMEN TO PREFERRED TLD REGIMEN IS LAGGING IN SUB-SAHARAN AFRICA

**Neha Shah**[1], Allahna Esber[2], Nicole Dear[2], Sean Cavannaugh[1], Michael Iroezindu[2], Emmanuel Bahemana[2], Hannah Kibuuka[1], John Owuoth[2], Jonah Maswai[1], Valentine Singoei[1], Trevor A. Crowell[1], Christina Polyak[1], Julie Ake[2]
[1]*Walter Reed National Military Medical Center, Bethesda, MD, USA,* [2]*Walter Reed Army Institute of Research, Silver Spring, MD, USA*

**Background:** Dolutegravir-based (DTG) regimens perform better than efavirenz-based regimens in maintaining viral suppression. In 2018, the World Health Organization recommended tenofovir disoproxil fumarate-lamivudine-dolutegravir (TLD) as the preferred first line regimen. While access was initially limited for women due to safety concerns in pregnancy, in 2019, DTG was shown to be safe in pregnancy and TLD became the WHO's preferred regimen for all populations. Nevertheless, final eligibility is determined by local policies. We examined TLD transition by gender across five PEPFAR-supported HIV care programs in sub-Saharan Africa.
**Methods:** The African Cohort Study (AFRICOS) enrolls people living with HIV (PLWH) engaged in care in Uganda, Kenya (South Rift Valley [SRV] and Kisumu West [KKW]), Tanzania and Nigeria. Participants come to clinic for exams, testing and medications every six months. PLWH on TLD at last study visit were included. We generated Kaplan-Meier (KM) curves to compare TLD transition by gender from 1) time of country rollout and 2) time of TLD eligibility according to local policies. Multivariable Cox proportional hazard models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for the association between gender and TLD transition, controlling for study site, age, and viral suppression.
**Results:** As of June 1, 2021, 1799 participants had at least one visit on TLD. Women (67.8%) were less likely than men (79.6%) to be on TLD at their last visit ($p<0.001$). Time to transition varied by site, with women in Tanzania transitioning at the same rate as men. In Nigeria, women initially had a slower transition but caught up to men. After adjusting for local policies, women in KKW transitioned at the same rate as men. In SRV and Uganda, women were less likely to be transitioned (Figure). In adjusted analysis, women in Uganda (aHR: 0.31; 95% CI: 0.24-0.41) and Kenya (SRV aHR: 0.37; 95% CI: 0.3 – 0.46; KW aHR: 0.48; 95% CI: 0.38 – 0.60) had a lower aHR of transitioning.
**Conclusion:** Despite TLD being the WHO's preferred regimen since 2019, transition of women to potentially life-saving TLD has been slower than men at certain clinical sites even after accounting for local eligibility criteria. Despite the same local policies, SRV transitioned slower than KKW. Education and quality improvement projects are ongoing to ensure eligible PLWH are on TLD. Further studies should be done to understand barriers to TLD transition.




## 896 HIV TEAMS AS TOOL TO IMPROVE THE HIV TESTING CASCADE IN HOSPITALS: #AWARE.HIV PROJECT

New Investigator Scholar

**Carlijn Jordans**[1], Kathryn S. Hensley[1], Jeroen J. van Kampen[1], Femke P. Mollema[2], Elisabeth H. Gisolf[3], Rachida El Moussaoui[4], Gonneke Hermanides[5],

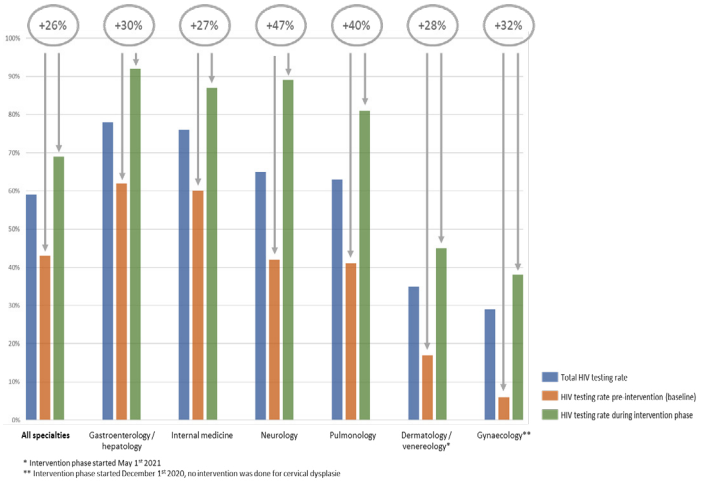
Anna Roukens[6], Robert-Jan Sips[7], Zoltán Szlávik[8], Renee N. Finkenflügel[9], Bart J. Rijnders[1], Annelies Verbon[10], Casper Rokx[1]
*[1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Medisch Centrum Haaglanden, The Hague, Netherlands, [3]Rijnstate Hospital, Arnhem, Netherlands, [4]Maasstad Hospital, Rotterdam, Netherlands, [5]Rode Kruis Ziekenhuis, Beverwijk, Netherlands, [6]Leiden University Medical Center, Leiden, Netherlands, [7]MyTomorrows, Amsterdam, Netherlands, [8]DAGNÄ eV, Berlin, Germany, [9]Academic Medical Center, Amsterdam, Netherlands, [10]University Medical Center Utrecht, Utrecht, Netherlands*

**Background:** In the Netherlands the majority of patients newly diagnosed with HIV are late presenters and had multiple prior missed opportunities to test for HIV. To end the epidemic, adequate testing of patients with HIV indicator conditions (ICs) is key to reduce the number of people unaware of their HIV diagnosis. #aware.hiv focusses on improving the first steps of the HIV testing cascade by adequate identification and HIV testing practices of patients with HIV ICs.

**Methods:** A single center prospective implementation project in Erasmus MC, The Netherlands. The primary objective was to evaluate the effect of HIV teams promoting HIV testing practices. A sensitive semi-automated hospital-wide HIV IC detection tool was developed to identify ICs using a two-step approach on electronically recorded ICD-10 and standardized health insurance codes (DBC). We recorded HIV IC prevalence and testing practices in a pre-intervention phase (January 2020-August 2020) followed by an intervention phase (August 2020 onwards) with a stepwise introduction of HIV teams per specialty. The multi-angle intervention included proactive testing recommendations from the HIV team for physicians treating HIV IC patients. We assessed the screening tool's output, HIV IC prevalence and HIV testing practices.

**Results:** Pre-intervention and during intervention (until August 2021) 137.520 new diagnoses were registered. Of these 11.734 (8,5%) diagnoses were flagged as possible HIV ICs. 451 were excluded for analysis, mainly due to death of patients or already being diagnosed with HIV. Manual cross-checking identified 1.346 HIV ICs (529 pre-intervention and 817 during intervention) of which 580 (43%) were not adequately tested for HIV. Five (0,7%) of the 766 adequately tested HIV ICs were found positive for HIV. Overall, pre-intervention and during intervention the proportion ICs that were adequately tested were 225/529 (43%) and 566/817 (69%) respectively. In specialties where HIV team interventions started immediately, HIV testing rates increased from a range of 41-62% to 81-92%, whilst testing rates increased from a range of 6-17% to 38-45% in specialties where HIV team interventions had a delayed start (figure 1). Proactive testing recommendations were given 81 times, resulting in 25 extra adequately tested HIV ICs.

**Conclusion:** The implementation of HIV teams can promote HIV IC identification and increase adequate HIV IC guided HIV testing in hospitals. This supports the further expansion of the project to assess its effectiveness.




## 897 PARTNER TESTING WITH HIV SELF-TEST DISTRIBUTION BY UGANDAN PREGNANT WOMEN WITH HIV

**Andrew Mujugira**[1], Gabrielle Stein[2], Agnes Nakyanzi[1], Jade Boyer[2], Deborah Donnell[2], Faith Naddunga[3], Paul Ssendiwala[1], Juliet Kyomugisha[3], Juliet Erone[3], Michelle Bulterys[2], Monisha Sharma[2], Monique A. Wyatt[4], Norma Ware[4], Connie L. Celum[2]
*[1]Infectious Diseases Institute, Kampala, Uganda, [2]University of Washington, Seattle, WA, USA, [3]Infectious Disease Institute, Kampala, Uganda, [4]Harvard Medical School, Boston, MA, USA*

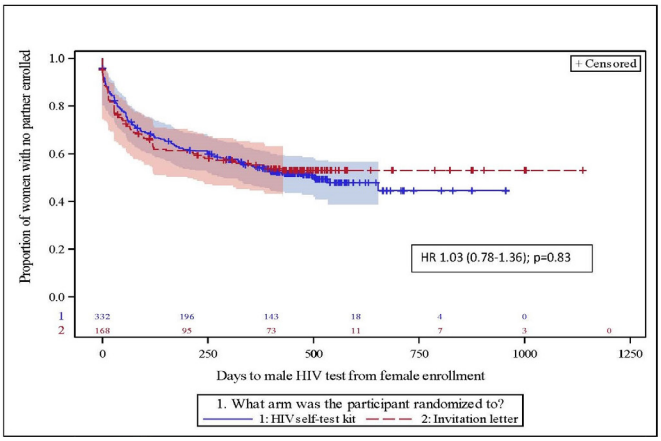
**Background:** Knowledge of HIV status and engagement in HIV prevention and care are lower for men than women in Africa. Secondary distribution of HIV self-test kits (HIVST) from HIV-negative pregnant women to their partners has been shown to be effective in increasing HIV testing coverage among partners. This strategy has not been evaluated among pregnant women living with HIV (PWLHIV), who may have distinct barriers to HIVST distribution.

**Methods:** In the Obumu study, 500 PWLHIV attending antenatal care in Kampala, Uganda who reported a partner of unknown HIV status were randomized 2:1 to HIVST secondary distribution or an invitation for fast-track HIV testing for their partner (NCT03484533). Men were offered confirmatory HIV testing at enrollment in Obumu and linkage to PrEP or ART depending on HIV status. Women and men were followed for 12 months post-partum. The co-primary outcomes were time to partner testing in clinic (evaluated using Cox proportional hazards), and men initiated on PrEP or ART by 12 months post-partum (evaluated using maximum likelihood), both analyzed as intention-to-treat (ITT).

**Results:** The median age of women was 27 years, 95% were married, 29% in a polygamous partnership, 96% on ART, 58% virally suppressed, and 82% of women reported giving the HIVST or invitation to their partner. Of the 234 men enrolled and tested for HIV, 159 (48%) were partners of PWLHIV in the HIVST arm and 75 (45%) in the invitation arm (HR for HIV testing=1.0, 95%CI 0.8-1.4). Of enrolled men, 49/234 (21%) tested HIV-positive. In the HIVST arm, 58/123 HIV-negative men (47%) accepted PrEP and 25/36 (69%) HIV-positive men accepted ART compared to 34/62 (55%) HIV-negative men and 10/13 (77%) HIV-positive men in the invitation arm. Assuming male partners who did not enroll were not on ART/PrEP, the ITT analysis of all men showed no difference in linkage to PrEP or ART by arm, with 104/328 (32%) of partners of PWLHIV in the HIVST arm and 53/161 (32%) in the invitation arm linked to ART or PrEP (p=0.8).

**Conclusion:** Secondary distribution of HIVST by Ugandan PWLHIV was not more effective in achieving HIV testing or linkage to ART or PrEP among partners compared to an invitation for fast-track HIV testing. Almost half of male partners of PWLHIV were tested for HIV at the site, higher than 17-25% in public programs. Additional strategies, such as outreach to partners of pregnant women by 'peer fathers' need to be evaluated for their effectiveness in increasing male partner HIV testing and linkage to PrEP and ART.

Fig 1. Days to Male HIV testing at site from Female Enrollment into the Obumu study, Kaplan-Meier curve




## 898 CONTRIBUTIONS TO THE DECLINE IN HIV INCIDENCE AMONG GBM IN THE UK: A MODELLING STUDY

**Valentina Cambiano**[1], Fiona Lampe[1], Alec Miners[2], Sheena McCormack[1], Noel Gill[3], Graham Hart[1], Kevin Fenton[4], Marc Thompson[5], Gus Cairns[6], Valerie Delpeche[7], Alison Rodger[1], Andrew N. Phillips[1]
*[1]University College London, London, UK, [2]London School of Hygiene & Tropical Medicine, London, UK, [3]Public Health England, London, UK, [4]Office of the Global AIDS Coordinator, Washington, DC, USA, [5]The Love Tank CIC, London, UK, [6]National Academy of Medicine Publications, London, UK, [7]United Kingdom Health Security Agency, London, UK*

**Background:** In the UK, HIV incidence among gay and bisexual men (GBM) has decreased substantially. Our aim was to understand the contribution to this

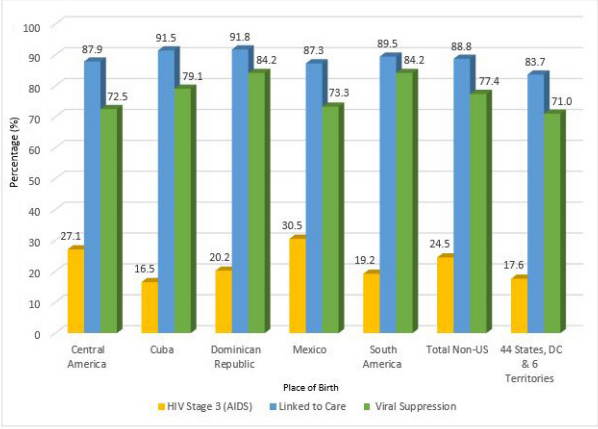
of the different components of combination prevention, and to estimate the impact on HIV incidence going forward of continuation of current policies.
**Methods:** We calibrated a dynamic, individual-based stochastic model, the HIV Synthesis Model, to multiple sources of data on HIV among GBM in the UK. We compared HIV incidence in 2020 with the counter-factual incidence if: (1) from 2013 condom use was low, i.e. at levels similar to those observed in 1980; (2) the HIV testing rate had remained stable from 2013; (3) the policy of antiretroviral treatment (ART) at diagnosis (as opposed to CD4 count < 350/$mm_3$) was not introduced in 2015, and (4) a Pre-exposure Prophylaxis (PrEP) strategy had not been introduced (through the PROUD and IMPACT trials, self-sourcing, and lately commissioning) with consequent lower levels of testing (recommended three monthly on PrEP) and ART initiation. We also projected future outcomes under the assumption of continuation of current policies.
**Results:** The intervention that had the biggest impact on HIV incidence by 2020 was PrEP, followed by ART at diagnosis. If either of these had not been introduced (but other interventions had been as implemented), HIV incidence in GBM in 2020 would have been respectively 52% and 22% higher than estimated in the scenario with the implementation of all components of combination prevention. Our results suggest that the HIV epidemic among GBM in the UK is on course to eliminate HIV with an incidence rate of 1.7/1,000 person-years in GBM aged 15-64 (90% range: 0.6 – 4.8/1,000 person-years) in 2020, declining to 0.55 (90% range: 0.25 -1.3) per 1,000 person-years in 2030 and to 0.23 (90% range: 0.11 - 0.54) per 1,000 person-years by 2040.
**Conclusion:** Since 2013, combination prevention, including widespread availability of PrEP, played a major role in the reduction in HIV incidence observed in the UK among GBM. Continuation of current prevention policies should lead to HIV elimination among GBM in the UK.

## 899 HIV CARE OUTCOMES BY PLACE OF BIRTH AMONG HISPANIC/LATINO PERSONS WITH HIV INFECTION

**Sonia Singh**[1], Tebitha Mawokomatanda[1], Eduardo Valverde[1]
*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA*

**Background:** In 2019, non-US-born persons accounted for 27% of all HIV diagnoses among Hispanic/Latino persons in the US. Assessing HIV care outcomes by place of birth (POB) is critical for targeted culturally appropriate prevention efforts and to elucidate which subgroups could benefit from increased testing and improvement in HIV care outcomes.
**Methods:** Data from 45 National HIV Surveillance System sites with complete laboratory reporting submitted to CDC through December 2020 were used to determine the numbers of Hispanic/Latino persons aged ≥13 years with an HIV diagnosis during 2019, the percentages of HIV stage 3 (AIDS) at diagnosis, linked to care within 1 month after diagnosis and virally suppressed within 6 months of diagnosis in 2019. Data were stratified by POB, sex, age and transmission category. POB was defined as Central America, Cuba, Dominican Republic, Mexico, South America and the US (born in the 50 states, DC or 6 US territories).
**Results:** Among 6,233 Hispanic/Latino persons with reported POB and an HIV diagnosis during 2019, for non-US-born POB (n=2,830), 33.7% were born in Mexico, 26.2% in South America, 21.6% in Central America, 12.0% in Cuba and 6.5% in Dominican Republic. Overall, 24.5% of non-US-born Hispanic/Latino persons with an HIV diagnosis were stage 3 (AIDS) at diagnosis compared to 17.6% of US-born. Mexican-born (30.5%) persons had the highest proportion of stage 3 (AIDS) at diagnosis. All sex and transmission categories for non-US-born Hispanic/Latino persons had higher percentage of HIV stage 3 (AIDS) at diagnosis compared to US-born. Overall, 88.8% of non-US-born Hispanic/Latino persons were linked to care compared to 83.7% US-born. The lowest percentage of persons linked to care was among US-born. Overall, 77.4% of non-US-born Hispanic/Latino persons achieved viral suppression (VS) compared to 71.0% of US-born. US-born had the lowest percentage of VS among all Hispanic/Latino persons.
**Conclusion:** Non-US-born Hispanic/Latino persons had higher HIV stage 3 (AIDS) diagnoses than US-born Hispanic/Latino persons. Targeted testing efforts for the non-US born Hispanic/Latino persons should be promoted, including culturally sensitive content, to increase early detection of HIV for improving awareness and reducing risk for HIV transmission. Likewise, healthcare providers should increase efforts to promote linkage to care and VS among US-born Hispanic/Latino persons, who are lagging in these health indicators, to improve HIV care outcomes among this group.

Figure. HIV Stage 3 (AIDS) at Time of Diagnosis of HIV infection and HIV Care Outcomes Among Latino/Hispanic Persons Aged ≥13 years with a Diagnosis of HIV Infection During 2019, by Place of Birth — 44 States and District of Columbia




Stage 3 (AIDS) at time of HIV diagnosis was determined by using the first CD4 test result or documentation of an AIDS-defining condition ≤3 months after the HIV diagnosis date during 2019.

Linkage to HIV medical care within 1 month after HIV diagnosis was measured by documentation of ≥1 CD4 (count or percentage) or viral load tests performed ≤ 1 month after HIV diagnosis, including tests performed on the same date as the date of diagnosis during 2019.

Viral suppression was defined as a viral load result of <200 copies/mL at any viral load test within 6 months of an HIV diagnosis made during 2019.

## 900 FIDELITY OF UNIVERSAL HIV TEST AND TREATMENT (UTT) IMPLEMENTATION IN SOUTH AFRICA

**Jabulani Ncayiyana**[1], Radoslaw Panczak[2], Per Von Groote[2], Matthias Egger[2]
*[1]University of KwaZulu-Natal, Durban, South Africa, [2]University of Bern, Bern, Switzerland*

**Background:** In 2016, the South African National Department of Health adopted World Health Organization (WHO) guidelines on universal HIV test and treatment (UTT), but evidence about UTT's implementation fidelity is limited. We aimed to describe timing of antiretroviral theraphy (ART) initiation and implementation fidelity of UTT guidelines in South Africa.
**Methods:** This was a prospective cohort study of ≥18-year-old HIV-positive patients who initiated ART under Treat-All in 6 participating International epidemiologic Databases to Evaluate AIDS (IeDEA) sites in South Africa from September 2016. For each UTT element, the proportion was calculated and multiplied by 100 to obtain the percentage representing the implementation fidelity. The percentages were summarised as a median percentage to obtain the overall fidelity of UTT guidelines. There is no specific guidance to define the optimal fidelity, however, values between 80 and 100% are typically considered high fidelity.
**Results:** Among 87,266 participants, the median age was 35 (IQR: 27–43) years. Approximately two thirds of participants were females (65.6%) and most had CD4 count of ≤200 cells/m3 (78%) Over half (53.2%) initiated same-day ART. Two thirds (67,3%) of those initiating same-day ART were men and 56.9% were still in care 6-12 months after ART initiation. The average level of fidelity was 77%, with variability by elements (19-79%) and site (21-86%). The elements with the highest fidelity were immediate priority and fast track initiation. ART initiation in TB co-infection had the lowest fidelity (27.3%). Fidelity differed by site.
**Conclusion:** Our study suggests moderate fidelity of implementation of UTT guidelines in South Africa. Our findings show the need to improve UTT guidelines implementation and further research exploring context-specific barriers to optimal implementation of UTT in different settings.

Table 1. Implementation Fidelity (adherence) of UTT guidelines stratified by IeDEA sites in South Africa.

| UTT policy element | Site | AfA | Gugulethu | Khayelitsha | Khethimpilo | Thembelethu | Tygerberg | Adherence (%) | Level of Fidelity* |
|---|---|---|---|---|---|---|---|---|---|
| | Site type | N/A | Clinic | Clinic | Clinic | Hospital | Hospital | | |
| | Site location | N/A | Urban | Urban | Rural | Urban | Urban | | |
| | Content | | | | | | | | |
| Immediate priority | Those with a CD4 count ≤ 350 cells/mm3 | 86.4 | 54.7 | 31.9 | 78.8 | 53.7 | 22.5 | 78.8 | Moderate |
| | Pregnant and breastfeeding women with no active TB or contraindications to FDC (TDF/FTC/EFV) | - | - | 42.6 | - | 61.5 | - | 50.0 | Low |
| Fast track initiation | Those with a CD4 count ≤ 200 cells/mm³ | 84.1 | 39.5 | 20.7 | 68.5 | 37.1 | 15.9 | 68.8 | Moderate |
| | Those at HIV stage 4 | 84.6 | 35.6 | 14.0 | 57.6 | 32.7 | 9.4 | 63.8 | Moderate |
| ART initiation in case of TB | Patient with TB, TB treatment should be started first followed by ART as soon as possible and within eight weeks | 9.5 | - | 57.4 | - | 20.0 | 50.0 | 19.0 | Low |
| | Patient has a CD4 count < 50 cells/mm³ ART should be initiated within two weeks after starting TB treatment, when the patient's symptoms are improving, and TB treatment is tolerated | 10.9 | - | 66.9 | - | 33.3 | 82.1 | 22.6 | Low |
| | If a patient has a CD4 > 50 cells/mm³ ART should be initiated within 2 – 8 weeks after starting TB treatment | 13.4 | - | 92.7 | - | 51.7 | 96.4 | 30.2 | Low |
| | Overall | 86.1 | 53.3 | 30.4 | 77.3 | 53.6 | 20.6 | 77.3 | Moderate |

*Levels of adherence 80–100% "high", 51–79% "moderate" and 0–50% "low" fidelity.

## 901 IMPACT OF AGING IN HIV ON COVID-19 OUTCOMES VIA A MATCHED STUDY

**Siyuan Guo**[1], Jiajia Zhang[1], Xueying Yang[1], Sharon Weissman[1], Bankole A. Olatosi[1], Rena Patel[2], Xiaoming Li[1]
[1]**University** of South Carolina at Columbia, Columbia, SC, USA, [2]University of Washington, Seattle, WA, USA

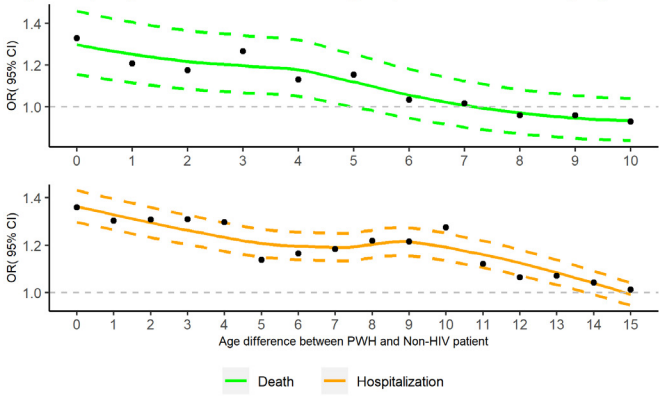
**Background:** HIV infection might accelerate aging process and people living with HIV (PLWH) have been observed to have a higher risk of severe COVID-19 outcomes. However, it is unclear whether the worse COVID-19 outcomes can be attributed to the accelerated aging process. This study aimed to examine: 1) the causal effect of HIV infection on severe COVID-19 outcomes; and 2) the threshold of age difference at which PLWH and non-HIV patients will have comparable COVID-19 outcomes.

**Methods:** We identified COVID-19 positive adults between Jan 1, 2020, and Oct 18, 2021, from the U.S. National COVID Cohort Collaborative (N3C), a nationally-sampled electronic medical record repository. We identified PLWH by clinical diagnosis, drug exposure, and laboratory results. Among COVID-19 cases, PLWH were matched 1:1 to non-HIV persons using exact matching (by gender, race, and ethnicity) and propensity score matching (PSM) (by age, gender, race, ethnicity, and pre-COVID comorbidities). To determine age threshold, PLWH were matched to older non-HIV patients with an age differences between 1 to 15 years. We used conditional logistic regression for exact matched data and standard logistic regression for PSM data. Subgroup analyses stratified by CD4 counts (≥200 or CD4<200 cells/mm$^3$) were also conducted.

**Results:** Among a total of 2,422,870 COVID-19 positive adults, we identified 15,188 PLWH. Among PLWH with CD4 data, 872 (14.03%) had CD4<200. Using exact match, PLWH had a significantly higher odds of COVID-19-associated hospitalization [OR: 1.95, 95%CI:(1.88,2.02)] or death [OR: 2.05, 95%CI:(1.90,2.22)] compared to non-HIV persons. By repeating PSM modeling with incrementally increasing ages, PLWH persistently had a higher risk of death compared to non-HIV persons until the age difference reached 6 years, while the threshold of age difference for the comparable hospitalization outcome extended to 14 years. Furthermore, when matching PLWH with CD4<200 with non-HIV persons, the threshold of age difference increased to 10 years for similar odds of mortality and at least 15 years for similar odds of hospitalization. PLWH with CD4≥200 more likely to be hospitalized, though had similar outcomes for death, than non-HIV persons.

**Conclusion:** We find that the worse COVID-19 outcomes, among PWH may be potentially related to aging in HIV. Further investigation of the biological mechanisms at the intersections of HIV infection itself (eg, lower CD4 counts) and accelerated aging in HIV causing worse COVID-19 outcomes is needed.

*Figure 1. Impact of HIV on COVID-19 outcomes using multiple PSMs at an increment age difference*




## 902 SIMILAR SHORT-TERM OUTCOMES WITH SAME-DAY ART INITIATION VS RAPID ART INITIATION

**Yi-Chia Huang**[1], Chia-Jui Yang[2], Yuan-Ti Lee[3], Hsin-Yun Sun[4], Chin-Shiang Tsai[5], Nan-Yao Lee[5], Po-Huang Liu[6], Hung-Jen Tang[7], Chen-Hsiang Lee[8], Chi-Ying Lin[9], Chien-Ching Hung[4]
*[1]National Taiwan University Hospital Hsin-Chu Branch, Hsinchu County, Taiwan, [2]Far Eastern Memorial Hospital, New Taipei City, Taiwan, [3]Chung Shan Medical University Hospital, Taichung, Taiwan, [4]National Taiwan University Hospital, Taipei, Taiwan, [5]National Cheng Kung University Hospital, Tainan, Taiwan, [6]Hsinchu Mackay Memorial Hospital, Hsinchu, Taiwan, [7]Chi Mei Medical Center, Tainan, Taiwan, [8]Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [9]National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, Taiwan*

**Background:** Taiwan CDC has implemented rapid ART initiation (ART initiation within 7 days of confirmed HIV diagnosis) program to improve HIV care continuum since 2018. In 2020-2021, same-day ART initiation was implemented with the introduction of immunochromatographic testing to expedite the confirmation of HIV infection. This study aimed to evaluate the short-term outcomes with same-day ART initiation vs rapid ART initiation.

**Methods:** Between 2018 and 2021, medical records of newly diagnosed people living with HIV (PLWH) were reviewed to collect the information on the dates of HIV diagnosis, ART initiation, and loss to follow-up; and sexually transmitted infections (STIs), plasma HIV RNA load (PVL) and CD4 count. All patients were followed for 48 weeks after ART initiation. Same-day and rapid ART initiation were defined as ART initiation within 1 day and 2-7 days of confirmed HIV diagnosis, respectively. The primary outcome was the proportion of patients engaged in care at Week 48. The secondary outcomes were the proportion of PVL <200 copies/ml at Week 4, 28 and 48, and occurrences of STIs before Week 48.

**Results:** 600 people were newly diagnosed with HIV infection during the study period. Their mean age was 32.6 (SD 9.4) years, 93.0% were MSM, 38.7% had CD4 counts <200 cells/mm$_3$ and 49.8% had plasma HIV RNA >5 log$_{10}$ copies/ml. Overall, 470 (78.3%) PLWH initiated ART within 7 days of HIV diagnosis: 252 (42.0%) on the same day and 218 (36.3%) within 2-7 days of diagnosis. Before Week 48, 7 (1.5%) PLWH died and 16 (3.4%) were lost to follow-up. Before Week 48, the rates of loss to follow-up were 3.2% and 3.7% for PLWH in the same-day ART initiation and rapid ART initiation group, respectively (p=0.804) (Table). The proportions of viral suppression of PLWH having undergone plasma HIV RNA testing were 68.4%, 94.7% and 98.5% at Week 4, 28 and 48 for PLWH who initiated ART on the same day of HIV diagnosis, compared to 71.4%, 98.1% and 97.1% for those who initiated ART within 2-7 days of diagnosis (p=0.530, 0.140, and 0.265, respectively). The proportions of STI diagnosed before Week 48 were similar between the two groups (p=0.669).

**Conclusion:** Our study demonstrated a low rate of loss to follow-up in PLWH who initiated ART within 7 days of confirmed HIV diagnosis. ART initiation on the same day of HIV diagnosis achieved a similar rate of retention in care and viral suppression to ART initiation within 2-7 days of diagnosis.

Table. Outcomes of people living with HIV who were put on same-day vs rapid ART initiation

| | Same-day initiation (n=252) | Rapid ART initiation (excluding same-day ART initiation) (n=218) | p-value |
|---|---|---|---|
| **Primary outcomes** | | | |
| Retention in care, n (%) | 218 (86.5) | 199 (91.3) | 0.182 |
| Death, n (%) | 6 (2.4) | 1 (0.5) | 0.129 |
| Transfer of care, n (%) | 20 (7.9) | 9 (4.1) | 0.088 |
| Loss to follow-up, n (%) | 8 (3.2) | 8 (3.7) | 0.804 |
| Virologic failure, n (%) | 0 | 1 (0.5) | 0.466 |
| **Secondary outcomes:** Retention in care with viral suppression (<200 copies/ml) | | | |
| Week 4 | 68.4% | 71.4% | 0.530 |
| Week 28 | 94.7% | 98.1% | 0.140 |
| Week 48 | 98.5% | 97.1% | 0.265 |
| Any STI before Week 48 | 11.1% | 12.4% | 0.669 |

## 903 RETENTION IN HIV CARE IN RURAL SOUTH AFRICA USING DATA HARMONIZATION APPROACHES

**Collins Iwuji**[1], Kathy Baisley[2], Dickman Gareta[3], Theresa Smit[3], Mark Siedner[3], Kobus Herbst[3]

*[1]University of Sussex, Brighton, UK, [2]London School of Hygiene & Tropical Medicine, London, UK, [3]Africa Health Research Institute, Mtubatuba, South Africa*

**Background:** Retention in care (RIC) and sustained viral suppression are key program indicators and prerequisites to achieving good health for people with HIV. Estimates of these indicators are susceptible to bias from poor record keeping and transfers from care. We examined RIC among adults aged ≥15 years in uMkhanyakude District who initiated antiretroviral therapy (ART) in 2013-2017.

**Methods:** Individuals were considered retained if they had a clinic visit recorded in the electronic ART database (TIER.net) in the past 6 months, or were recorded as having transferred out. We used Kaplan Meier methods to estimate RIC based on TIER.net alone. We then corrected estimates of RIC to account for poor record keeping or clinic transfers using information from two data sources: drug levels and viral load on dried blood spots from an annual HIV serosurvey conducted in the area and viral load data from a community-based multimorbidity study.

**Results:** 3202 (79% female) individuals who initiated ART during 2013-2017 were included in the analysis. Based on TIER.Net data alone, RIC at 5 years was 60.4% (95%CI=57.8-62.9%), and slightly lower in women than men (59.5%, 95%CI 56.5-62.3% vs 63.9%, 95%CI 58.4-68.8%). After correcting for community-based data collection, RIC at 5 years was 89.5% (CI=87.4-91.6%). Risk of death was 2.2%, based on TIER.net alone, vs 5.2% using mortality data from community-based data.

**Conclusion:** TIER.net registers appear to vastly underestimate RIC and underestimate mortality for people with HIV on ART. Development and implementation of a National Electronic Health Record System and/or upgrading the TIER.net system to include cross-clinic communication about patient transfers and/or consolidating individual health records is likely to improve patient care and promote more valid estimates of key clinical indicators to optimize allocation of resources.

## 904 WITHDRAWN

## 905 RETURN TO CARE AFTER INTERRUPTION IN TREATMENT IN SOUTH-CENTRAL UGANDA

**Alice Kisakye**[1], Edward N. Kankaka[1], Joseph Kabanda[2], Bill Elur[2], Rose B. Nakityo[2], Steven J. Reynolds[3], M Kate Grabowski[4], Maria Wawer[5], Ronald Gray[5], Larry W. Chang[5], Fred Nalugoda[1], Gertrude F. Nakigozi[1], Joseph Kagaayi[1], David Sserwadda[1]

*[1]Rakai Health Sciences Program, Kalisizo, Uganda, [2]Centers for Disease Control and Prevention, Kampala, Uganda, [3]National Institutes of Health, Bethesda, MD, USA, [4]The Johns Hopkins University, Baltimore, MD, USA, [5]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*

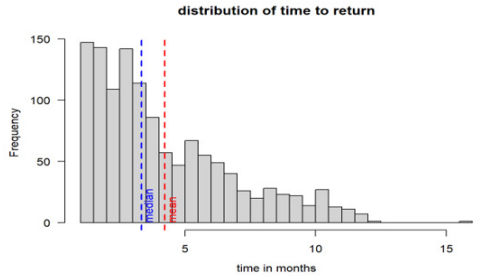
**Background:** Antiretroviral therapy (ART) reduces HIV-related morbidity and mortality and is essential for epidemic control. To prevent interruptions in treatment (IIT), the Masaka Region HIV Program in south-central Uganda, under PEPFAR funding, implemented client-centered care including differentiated service delivery models (DSD), appointment tracking systems, and psychosocial support. However, IIT remain a challenge. We studied correlates of return and time to return to care among clients with IIT.

**Methods:** We analyzed clients with IIT during January 1, 2020–March 31, 2021 receiving ART at 95 facilities in 12 districts. IIT was defined as no clinical contact for >28 days from missed appointment. Follow-up by home visits and/or phone calls commenced the day of missed appointment; outcomes (i.e. returned to care, self-transferred, migrated, died, unknown) up to May 1, 2021 were included. Descriptive statistics, logistic regression, and non-parametric tests of medians were conducted for correlates of return and time to return.

**Results:** Of 2,356 clients with IIT, 1,381 (59%) were women. Median age, ART duration and time to return were 35 years (interquartile range [IQR]: 27.2,41.7); 3.6 yrs (IQR: 1.4,6.0), and 3.3 months (IQR 2.1,5.9) respectively. Most clients 2,220 (94%) received ART in facility- vs. 6% in community-based settings; 2,128 (90%) were virologically suppressed (<1,000 copies/ml) prior to IIT. Outcomes were 1,266 (54%) returned to care, 116 (4.9%) self-transferred, 35 (1.5%) migrated, 20 (0.8%) died, 919 (39%) unknown. Return was more among: clients in facility-based models vs. community models (Odds Ratio [OR]: 4.34, Confidence Interval [CI]: 2.36–7.96, p<0.001); clients on ART for 4–6 yrs vs. those on ART < 2 yrs (OR: 1.70, CI: 1.13–2.56, p=0.011); and non-suppressed vs. suppressed clients prior to IIT (OR: 4.05, CI: 1.64-10.0, p=0.002). Time to return was longer in facility-based vs. community models (median 3.35 vs 2.97 months, p=0.032), and non-suppressed vs. suppressed clients prior to IIT (5.43 vs 3.23 months, p<0.001).

**Conclusion:** Almost 40% could not be traced. There were higher proportions but slower return in facility-based models; 75% returned clients returned within 6 months. It is important to consider more effective procedures to mitigate IIT especially in community-based treatment models and to act quickly once IIT

occurs among clients with VL-non-suppression pre-IIT and in facility-based clients.




## 906 SPATIAL HETEROGENEITY IN TREATMENT INTERRUPTION AND RETURN IN HIV PROGRAM IN UGANDA

**Edward N. Kankaka**[1], Alice Kisakye[1], Francis X. Wasswa[1], Fred Nalugoda[1], Joseph Kabanda[2], Grace Namayanja[2], Steven J. Reynolds[3], M. Kate Grabowski[4], Maria Wawer[4], Ronald Gray[4], Larry W. Chang[4], Gertrude F. Nakigozi[1], Joseph Kagaayi[1], David Serwadda[5]

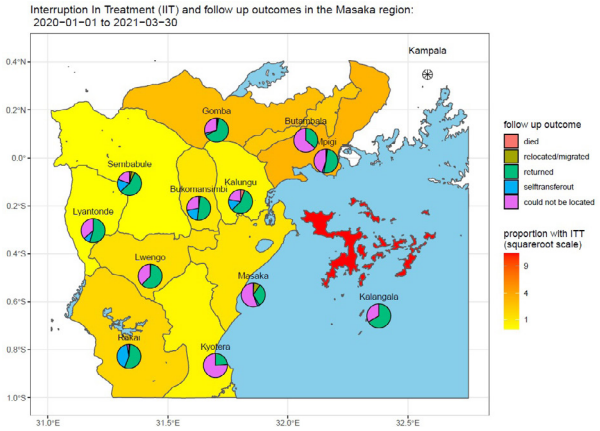
*[1]Rakai Health Sciences Program, Kalisizo, Uganda, [2]Centers for Disease Control and Prevention, Kampala, Uganda, [3]National Institutes of Health, Bethesda, MD, USA, [4]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [5]Makerere University College of Health Sciences, Kampala, Uganda*

**Background:** Highly-mobile populations may be at greater risk of interruptions in treatment (IIT), which can lead to higher rates of HIV-related morbidity and mortality. In south-central Uganda, prevention of IIT has mostly focused on highly-mobile groups. To understand mobility and IIT, we explored spatial correlation between IIT and client return to care in a PEPFAR-supported treatment program.

**Methods:** We analyzed clients with IIT during January 1, 2020–March 31, 2021 who received ART at 95 facilities in12 districts, who had follow-up outcomes (i.e., returned to care at the same facility, self-transferred, died, relocated/migrated [with no evidence of treatment], could not be located) by May 1, 2021. Proportions of IIT and return to care were calculated. The denominator for IIT proportions was the median number of clients active on treatment throughout this period, which is updated every quarter. High IIT was defined as more than district median IIT. High return was defined as return to care for >50% of those with IIT. Using Pearson correlation, we compared rates of IIT and return for the 12 districts. Data were analyzed in R (version 4.1.1).

**Results:** A total of 2,329 clients had IIT, of which 1244 (53%) returned to care; (n = 115, 4.9%) self-transferred; (n = 20, 0.9%) died; (n=35, 1.5%) relocated/migrated; and 915 (39%) could not be located. Median IIT was 1.2% (range = 0.4% [Sembabule] to 12.1% [Kalangala]). Islands or fishing communities and closer proximity to Uganda's capital (Kampala) had higher IIT compared to other districts. There was no correlation between rates of IIT and return (Pearson rho = 0.11, p = 0.745); 5 districts had high IIT and high return rates, 1 had high IIT with low return, 4 had low IIT with high return, and 2 had low IIT with low return.

**Conclusion:** IIT was higher in island fishing communities. However, rates of IIT did not correlate with return to care. It is important to consider both metrics in developing interventions to reduce discontinuity of care.




## 907 IMPACT OF BRAZILIAN HEALTH POLICIES ON GENDER/AGE GAPS IN HIV TREATMENT INDICATORS

**Felipe Krakauer**[1], Julie Somogyi[1], Fernanda M. Rick[2], Alexandre A. Ferreira[3], Vivian I. Avelino-Silva[3]

*[1]Faculdade Israelita de Ciências da Saúde Albert Einstein, Sao Paulo, Brazil, [2]Aids Healthcare Foundation, Sao Paulo, Brazil, [3]University of Sao Paulo, Sao Paulo, Brazil*

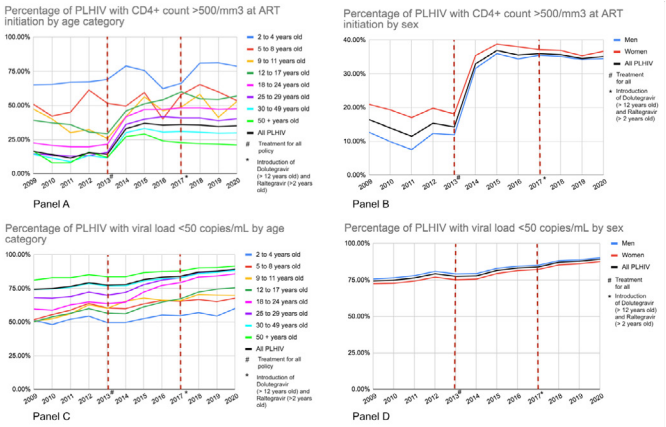
**Background:** Despite existing antiretroviral treatment (ART) options for people living with HIV (PLHIV), with universal and free-of-charge treatment available in Brazil, remaining gaps in HIV indicators by gender and age are still evident. Health policies can reduce such gaps. Monitoring the impact of heal

**Methods:** We used programmatic data from the Ministry of Health of Brazil to address temporal trends in timely initiation of ART (ART initiation at CD4+ count >500/mm$_3$) and viral load suppression (VLS; viral load <50 copies/mL among those under ART) between 2009-2020, according to age categories and gender. The effect of recent health policies - treatment for all (TFA, 2013); dolutegravir as a first-line therapy for all PLHIV >12 years old (2017); and raltegravir as a first-line therapy for children >2 years old (2017), was evaluated graphically.

**Results:** The study dataset included more than 757,000 PLHIV linked to care (with at least one ART dispensation or CD4+ measurement or viral load assessment) in 2020. Prior to the TFA policy, timely initiation of ART had important differences according to age and gender, with younger age categories and females receiving earlier treatment (Figure 1, Panels A and B). Although this gap has been reduced after the TFA policy, remaining heterogeneities are still evident, with lower percentages of older adults receiving timely ART (Panel A). We observed higher proportions of males and older PLHIV with VLS across the study period (Panels C and D); however, a gradual reduction in VLS gaps was observed since 2013 among PLHIV >12 years old, with slower improvements in the younger age groups (Panel C). Males had higher percentages of VLS compared to females; nonetheless, the difference in proportions of VLS by gender was small across the study period (Panel D).

**Conclusion:** Public health policies implemented in Brazil have reduced the gender and age gaps in treatment indicators. However, remaining gaps are still evident, with lower proportions of older patients receiving timely ART, and lower proportions of children and women achieving VLS. Additional policies, including the implementation of new treatment options in the pediatric regimens, dolutegravir for pregnant women and women planning to conceive, and the promotion of HIV screening and early ART initiation for older adults, could further reduce HIV treatment gaps in Brazil.

Figure 1: Temporal trends of timely initiation of antiretroviral therapy and viral load suppression by age and gender




## 908 POSITIVE PATHWAYS: IMPLEMENTATION TRIAL FOR HIV RETENTION IN CARE

**Michael Wohlfeiler**[1], Rachel P. Weber[2], Laurence Brunet[2], Jennifer S. Fusco[2], Christine Uranaka[1], Quateka Cochran[1], Monica Palma[1], Tammeka Evans[3], Carl Millner[1], Gregory P. Fusco[2]

*[1]AIDS Healthcare Foundation, Los Angeles, CA, USA, [2]Epividian, Durham, NC, USA, [3]ViiV Healthcare, Research Triangle Park, NC, USA*

**Background:** Only 50% of people with HIV (PWH) in 2019 were retained in care in the US. We evaluated whether alerts identifying PWH at-risk of falling out of care and prompts for enhanced contact were effective in retaining PWH in care in the US.

**Methods:** In this cluster randomized controlled trial (10/2020 to 7/2021), AIDS Healthcare Foundation Healthcare Centers (HCCs) were randomized to receive the intervention (n=10) or not (n=10); all maintained existing retention efforts. The intervention included automated alerts delivered in CHORUS™, a mobile app and web-based reporting solution utilizing electronic health record data (Table). After receiving an alert, staff and providers were prompted to re-engage at-risk PWH and schedule an appointment. Flags represented a consecutive period in which a PWH met criteria for ≥1 alert. Among PWH who received ≥1 flag, the association between the intervention and visits at any time or ≤2 months after a flag was assessed using logistic regression models fit with generalized estimating equations (independent correlation structure) to account for clustering. To adjust for differences between HCCs, models included census region, number of PWH at HCC, and proportions of PWH who self-identified as Hispanic or had Ryan White as a payer (Table).

**Results:** Of 15,875 PWH in care, 56% received ≥1 flag (Table). 90% (intervention) and 86% (control) of flags resulted in an appointment. 76% (intervention) and 75% (control) resulted in a visit, of which 25% were within 14 days and 76% were within 2 months of the flag. In adjusted analyses, over the 10-month study, flags were qualitatively more likely to result in a visit (aOR 1.08, 95% CI: 0.97, 1.21) or a visit within 2 months (aOR 1.07, 95% CI: 0.97, 1.17) at intervention than control HCCs. Among at-risk PWH with viral loads at both baseline and study end (i.e., PWH retained in care), the proportion with <50 copies/mL increased in both study arms, but more so at intervention (65% to 74%) than control (62% to 67%) HCCs.

**Conclusion:** Despite the challenges of a pandemic, adding an intervention to ongoing retention efforts, and the reality that behavior change takes time, PWH flagged as at-risk of falling out of care were marginally more likely to return for care at intervention than control HCCs and a greater proportion of them achieved undetectability. Sustained use of the retention module in CHORUS™ has the potential to streamline retention efforts, retain more PWH in care, and ultimately decrease transmission of HIV.

**Table. Characteristics of Healthcare Centers, People with HIV, and Alerts in the Positive Pathways Study**

| | Intervention Arm N=10 HCCs; 8836 PWH | Control Arm N=10 HCCs; 7039 PWH |
|---|---|---|
| HCCs in Southern US Census region, n (%) | 7 (70) | 5 (50) |
| Number of active[a] PWH per HCC, median (IQR) | 1081 (621, 1812) | 1018 (559, 1649) |
| Percentage of active[a] PWH with Hispanic/Latino ethnicity per HCC, median (IQR) | 18 (7, 34) | 20 (9, 23) |
| Percentage of active[a] PWH with ADAP/Ryan White as a payer per HCC, median (IQR) | 36 (23, 68) | 28 (19, 42) |
| Number of active[a] PWH who received ≥1 alerts, n (%) | 4977 (56) | 3888 (55) |
| Number of active[a] PWH who received ≥2 flags, n (%) | 1541 (17) | 1221 (17) |
| Total alerts, n | 8860 | 6878 |
| Alert #1: No clinical appointment in the previous 4 months and no scheduled clinical appointment in the next 2 months, n (%) | 2412 (27) | 1817 (26) |
| Alert #2: A single appointment in the previous year, with a missed clinical appointment in the previous month, and no scheduled appointment in the next 2 months, n (%) | 173 (2) | 143 (2) |
| Alert #3: Two missed sequential clinical appointments and no scheduled appointment in the next 7[b] days, n (%) | 3820 (43) | 3063 (45) |
| Alert #4: Lab result of >1,000 copies/mL >3 months ago without any evidence of a subsequent viral load < 20[c] copies/mL and no scheduled appointment in the next 7[b] days, n (%) | 2455 (28) | 1855 (27) |

ADAP, AIDS Drug Assistance Program; HCC, healthcare center; IQR, interquartile range; mL, milliliter; n, number; PWH, people with HIV; US, United States
[a] Active PWH were eligible to receive alerts and included PWH who were alive, aged ≥18 years, and in care (i.e., have had a visit with a healthcare provider or a lab measurement (HIV RNA or CD4 cell count) within the last 13 months prior to baseline date)
[b] As of April 2021, the acceptable window for a subsequent appointment was moved to 14 days following discussions with AHF retention leadership, due to the impracticality of scheduling patients within 7 days
[c] As of April 2021, the threshold for undetectability was changed from <20 copies/mL (i.e., test's limit of detection) to <50 copies/mL to better reflect standard of care

## 909 MODELING THE IMPACT AND COST-EFFECTIVENESS OF INTERVENTIONS FOR RETENTION IN HIV CARE

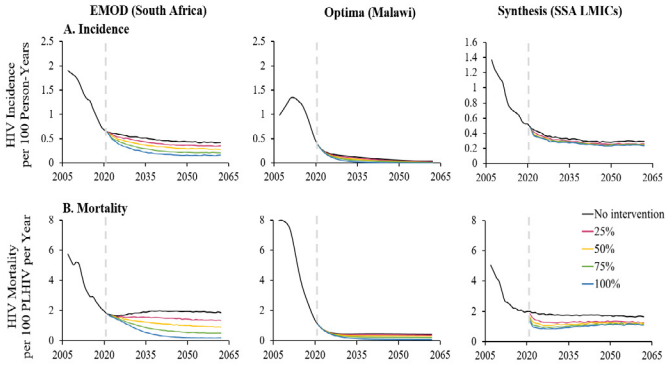
**Anna Bershteyn**[1], Lise Jamieson[2], Hae-Young Kim[1], Masabho P. Milali[1], Edinah Mudimu[3], Debra ten Brink[4], Rowan Martin-Hughes[4], Sherrie L. Kelly[4], Andrew N. Phillips[5], Loveleen Bansi-Matharu[5], Valentina Cambiano[5], Paul Revill[6], Gesine Meyer-Rath[2], Brooke Nichols[7]
*[1]New York University Grossman School of Medicine, New York, NY, USA, [2]University of Witwatersrand, Johannesburg, South Africa, [3]University of South Africa, Pretoria, South Africa, [4]Burnet Institute, Melbourne, Australia, [5]University College London, London, UK, [6]University of York, York, UK, [7]Boston University, Boston, MA, USA*

**Background:** Universal eligibility for antiretroviral therapy (ART) in sub-Saharan Africa (SSA) has reduced HIV transmissions and deaths among people living with HIV (PLHIV). A growing proportion of transmissions and deaths now occur among PLHIV who have interrupted ART. Dozens of interventions to improve retention on ART have been proposed, but most of them cost more than standard-of-care. Research is needed to inform the upper-bound costs at which such interventions should be adopted.

**Methods:** We used three HIV models with diverse structures, assumptions, and settings: EMOD in South Africa, Optima in Malawi, and Synthesis in SSA lower-middle income countries (LMICs). Each model simulated reducing ART interruptions by 25%, 50%, or 100%, with or without targeting those most-at-risk of interruption, and with annual discount rates of 0%, 3%, or 6%. We compared infections averted, disability-adjusted life-years (DALYs) averted, and upper-bound costs at which improving ART retention could be cost-effective compared to alternative HIV program investments.

**Results:** The three models simulated diverse epidemic trends and estimated different impact levels and timing of the impact of retention interventions (Figure 1). Despite these differences, the models produced consistent estimates of health benefit and transmission reduction per additional person-year retained on ART. The range of estimates was 1.35 – 2.60 DALYs and 0.07 – 0.16 infections averted over 40 years per additional person-year retained on ART over this period. Upper-bound cost that could be spent to retain an additional person on ART varied by setting and intervention effectiveness. Improving retention by 25% among all people receiving ART, regardless of ART interruption risk, had an upper-bound cost per person-year of US$2 – $6 per person-year in Optima (Malawi), US$43 – $68 in Synthesis (SSA LMICs), and US$28 – $180 in EMOD (South Africa). A maximally targeted and effective retention intervention had an upper-bound cost per person-year of US$93 – $223 in Optima (Malawi), US$871 – $1,389 in Synthesis (SSA LMICs), and US$1,013 – $6,518 in EMOD (South Africa).

**Conclusion:** Across diverse settings and assumptions, three HIV models provided consistent estimates of the health and transmission benefits of improving retention in SSA. Upper-bound costs that could be spent to improve ART retention vary across SSA settings and could be increased by targeting interventions to those most at-risk of interrupting ART.




## 910 LONGITUDINAL ANALYSIS OF ADAP UTILIZATION: 2008-2018

**Kathleen A. McManus**[1], Andrew Strumpf[1], Brian Sun[2], Amber Steen[2], Tim Horn[3], Auntré Hamp[3], Amy Killelea[4], Olivia Liu[2], Elizabeth T. Rogawski McQuade[5]
*[1]University of Virginia, Charlottesville, VA, USA, [2]University of Virginia, Charlottesville, VA, USA, [3]National Alliance of State & Territorial AIDS Directors, Washington, DC, USA, [4]Killelea Consulting, Arlington, VA, USA, [5]Emory University, Atlanta, GA, USA*

**Background:** AIDS Drug Assistance Programs (ADAPs) are a critical arm of the Ryan White HIV/AIDS Program (RWHAP) that enable uninsured/underinsured people with HIV (PWH) with low incomes access to HIV-related medications. While ADAPs continue to expand options for health insurance coverage and have documented effectiveness towards promoting viral suppression, no studies have analyzed longitudinal trends in client utilization. The objective of this study was to evaluate trends in ADAP utilization among key demographic subpopulations using national, regional, and state-level longitudinal data.

**Methods:** State-level data regarding ADAP client utilization were collected via the National Alliance of State and Territorial AIDS Directors (NASTAD) National RWHAP Part B and ADAP Monitoring Project reports for years 2008-2018. Estimated HIV prevalence data were collected from the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) AtlasPlus (2008-2018). Descriptive statistics were applied to estimate the overall proportion of PWH served by ADAP including demographic subpopulations (age, race/ethnicity, and sex). Linear mixed models were built to assess the proportion of clients served over time by the fixed effects of year and a binary, indicator term (i.e. <2015) to adjust for the increase in ADAP utilization following the elimination of programmatic waitlists in 2015 and the random effect of states.

**Results:** Of the estimated 1,020,450 PWH nationally in 2018, 234,798 (23%) were served by ADAP. This was a significant increase compared to 2008 in which 14% of the estimated 768,038 PWH were served. The proportion of PWH served by ADAP increased significantly over time (% change per year: 0.4%, 95% CI 0.2 – 0.6) with a large increase in 2015 (% change from 2014: 9.3%, 95% CI 7.7 – 10.9). PWH aged 13 – 24 experienced the largest increase in proportion

served (18%) when compared to those aged 25 – 44 and 45 or older (11% and 7%, respectively). Overall, ADAP utilization increased among each racial subpopulation. However, the uptick in White PWH was significantly higher (23%) when compared to Black or Hispanic PWH (11% and 9%, respectively), both at the national and regional level.

**Conclusion:** While ADAPs continue to expand coverage and provide support for uninsured/underinsured clients, there are disparities in client utilization among racial subpopulations on both a national and regional scale. Further study is warranted to assess the factors that contribute to this health inequity.

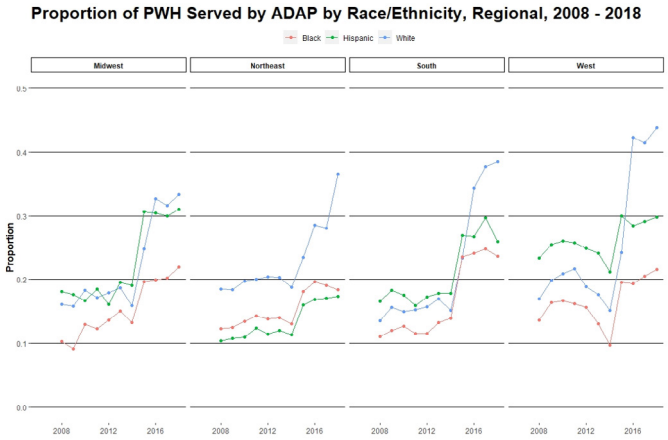



Figure 1: Proportion of PWH served by ADAP by race/ethnicity and region, 2008 – 2018. Regions defined by US Census Bureau. Calculated as the proportion of clients served (from NASTAD survey) out of all PWH (CDC prevalence data from CDC Atlas). Note: y-axis max is 50%.

## 911 VIRAL LOAD BEFORE SWITCHING TO DOLUTEGRAVIR & ASSOCIATION WITH HIV TREATMENT OUTCOMES

New Investigator Scholar

**Matthew L. Romo**[1], Jessie Edwards[2], Aggrey Semeere[3], Beverly Musick[4], Mark Urassa[5], Francesca Odhiambo[6], Lameck Diero[7], Charles Kasozi[8], Gad Murenzi[9], Patricia Lelo[10], Annette H. Sohn1[1], Kara Wools-Kaloustian[4], Denis Nash[1]
*[1]City University of New York, New York, NY, USA, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]Makerere University, Kampala, Uganda, [4]Indiana University, Indianapolis, IN, USA, [5]National Institute for Medical Research, Kisesa HDSS, Mwanza, Tanzania, United Republic of, [6]Kenya Medical Research Institute, Nairobi, Kenya, [7]Moi University, Eldoret, Kenya, [8]Masaka Regional Referral Hospital, Masaka, Uganda, [9]Rwanda Military Hospital, Kigali, Rwanda, [10]Kalembelembe Pediatric Hospital, Kinshasa, Congo, The Democratic Republic Of The, [11]TREAT Asia, amfAR, Bangkok, Thailand*

**Background:** Dolutegravir (DTG) is being rolled out globally as part of preferred antiretroviral therapy (ART) regimens, including among treatment-experienced patients. The clinical importance of viral load (VL) testing before switching patients already on ART to a DTG-containing regimen is less clear in real-world settings.

**Methods:** We included patients from the Central and East Africa regions of the International epidemiology Databases to Evaluate AIDS consortium who switched from a nevirapine- or efavirenz-containing regimen to a DTG-containing regimen and had ≥6 months of possible follow-up. We used multivariable, cause-specific hazards regression models to estimate the association between the most recent VL test in the 12 months before switching and five outcomes after DTG initiation: 1) incident VL ≥1000 copies/mL (with a subsequent VL ≥1000 copies/mL or lack of subsequent VL test); 2) pulmonary tuberculosis or WHO Clinical Stage 4 event; switch to a 3) protease inhibitor (PI)-containing regimen or 4) non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen; and 5) death or loss to program (LTP). Models included a random effect for site and were adjusted for age group, sex, prior AIDS diagnosis, and history of disengagement from care.

**Results:** We included 36,393 patients at 37 sites in 5 countries (Democratic Republic of the Congo, Kenya, Rwanda, Tanzania, Uganda) who switched to DTG between 7/2017 and 2/2020; median follow-up was 11 months. In the 12 months before switching, 88% of patients had a VL <200 copies/mL, 5% had a VL 200-399 copies/mL, 3% had a VL 400-999 copies/mL, 1% had a VL ≥1000 copies/mL, and 4% did not have a test. During follow-up, the most common outcomes were switching to an NNRTI-containing regimen (8.3 per 100 person-years) and death or LTP (4.1 per 100 person-years). Compared with patients who had pre-switch VLs <200 copies/mL, those with a pre-switch VL ≥1000 or without a pre-switch VL test were both significantly more likely to have an incident VL ≥1000 copies/mL, pulmonary tuberculosis or a WHO Clinical Stage 4 event, switch to an NNRTI-containing regimen, and death or LTP.

**Conclusion:** Patients who switched to DTG with a VL ≥1000 copies/mL or without a recent VL test had worse HIV treatment outcomes than those who switched with a VL known to be suppressed. These patients should receive additional monitoring and possibly adherence support during and after the programmatic transition to DTG to prevent differentially adverse outcomes.

HIV treatment outcomes after switching to dolutegravir and associations with pre-switch viral load status

| | Incident VL ≥1000 copies/mL* | Pulmonary TB or WHO Clinical Stage 4 event* | Switch to a PI-containing regimen | Switch to an NNRTI-containing regimen | Death or loss to program |
|---|---|---|---|---|---|
| Incidence rate per 100 person-years (95% CI) | 1.5 (1.4-1.6) | 0.3 (0.3-0.4) | 0.3 (0.3-0.4) | 8.3 (8.0-8.6) | 4.1 (3.9-4.3) |
| VL status before switching to dolutegravir, adjusted hazard ratio (95% CI) | | | | | |
| <200 copies/mL | Reference | Reference | Reference | Reference | Reference |
| 200-399 copies/mL | 1.61 (1.13-2.30) | 1.46 (0.53-4.04) | 1.35 (0.54-3.36) | 0.99 (0.82-1.20) | 1.14 (0.90-1.46) |
| 400-999 copies/mL | 1.75 (1.18-2.59) | 1.00 (0.25-4.11) | 2.72 (1.17-6.35) | 1.20 (0.97-1.49) | 1.12 (0.82-1.52) |
| ≥1000 copies/mL | 6.60 (4.36-9.99) | 13.97 (6.62-29.50) | 30.53 (17.87-52.18) | 2.83 (2.22-3.61) | 2.56 (1.81-3.63) |
| No viral load test | 2.89 (1.99-4.19) | 4.78 (2.77-8.24) | 2.13 (0.90-5.04) | 1.55 (1.31-1.83) | 3.77 (3.19-4.46) |

NA, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TB, tuberculosis; VL, viral load; WHO, World Health Organization. *Analysis limited to patients who had the outcome assessed.

## 912 MAINTAINED ACCESS TO PREVENTION & CARE FOR PWID DESPITE COVID-19 IN HAIPHONG, VIETNAM

**Delphine Rapoud**[1], Duc Q. Nguyen[2], Trang T. Nguyen[3], Huong T. Duong[2], Oanh T. Khuat[4], Nicolas Nagot[1], Don C. Des Jarlais[5], Khue M. Pham[2], Vinh H. Vu[6], Didier Laureillard[7], Mai S. Le[2], Laurent Michel[8], Jean-Pierre Molès[1], Thanh T. Nham[4], Giang T. Hoang[2]
*[1]Institut National de la Santé et de la Recherche Médicale, Montpellier, France, [2]Hai Phong University of Medicine and Pharmacy, Hai Phong, Viet Nam, [3]Hanoi Medical University, Hanoi, Vietnam, [4]Center for Supporting Community Development Initiatives, Hanoi, Viet Nam, [5]New York University, New York City, NY, USA, [6]Viet Tiep Hospital, Hai Phong, Vietnam, [7]Centre Hospitalier Universitaire de Nimes, Nimes, France, [8]Institut National de la Santé et de la Recherche Médicale, Paris, France*

**Background:** Haiphong is a Vietnamese city of 2 million people and a historic hotspot for HIV and drug use. The DRIVE community research program recently demonstrated the end of the HIV epidemic among PWID in the city, with an incidence of 0.085/100PY, and a substantial decrease in HCV incidence in the past 5 years. After the emergence of COVID-19, a one-month strict lockdown was imposed in April 2020 in Vietnam, followed by lighter social distancing restrictions over the year. We investigated whether those measures affected PWID in terms of risk behaviors and access to prevention and care.

**Methods:** Participants were PWID that had been enrolled in a respondent-driven sampling (RDS) survey as part of DRIVE in the last quarter of 2019. They were recalled and interviewed in the last quarter of 2020 by peer educators on their socioeconomic situation, drug use and sexual behaviors, relations to methadone maintenance treatment (MMT) and ART services. They were tested for drugs and methadone in the urine, and for HIV, HCV, and HIV plasma viral load when HIV(+). Changes following the restrictions were assessed by comparing these "after" data to the "before" data collected one year earlier during the RDS survey. In-depth interviews were conducted with 30 participants including 5 female sex workers (FSW).

**Results:** 780 PWID were enrolled. Their mean age was 44 years and 94% were male. 56% were still actively injecting (100% heroin) at the time of the interview; their monthly consumption had decreased from 24 to 17 days on average. The main source of syringes remained pharmacies for 83% before, during and after the lockdown. The proportion of PWID still engaging in sharing decreased from 6.0 to 1.5%. No change in the frequency of condom use was reported. The proportion of PWID on MMT increased from 68.7 to 75.3%. There was no alteration in the HIV cascade of care that was still above 90/90/90. No HIV seroconversion was observed, and HCV incidence remained stable (2.6/100PY, 95%CI: 0.7-6.7). 53% reported a monthly income of less than 130 USD "after" compared to only 9% "before". One FSW reported accepting unsafe sex during the lockdown due to financial pressure.

**Conclusion:** Six months after the beginning of COVID-19-related restrictions, access to harm reduction materials and care services for PWID was maintained and no increase in the number of new HIV or HCV infections was observed. However, this period was a major financial challenge, especially for FSW that were more likely to engage in risky sexual behaviors.

## 913 SUBSTANCE USE AND HIV OUTCOMES AMONG PRISON RELEASEES IN ZAMBIA: A COHORT STUDY

**Michael E. Herce**[1], Helene J. Smith[2], Vivien Mai[3], Chilambwe Mwila[4], Mirriam Nanyangwe[4], Lillian Kashela[4], Tina Kayumba[4], Yotam Lungu[4], Clement Moonga[4], Sisa Hatwiinda[4], Stewart E. Reid[4], Monde Muyoyeta[4]
*[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]University of New South Wales, Sydney, Australia, [3]University of Toronto, Toronto, Canada, [4]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia*

**Background:** Little is known about HIV outcomes and risk factors for poorly controlled HIV disease in PLHIV returning to the community after incarceration ("releasees") in sub-Saharan Africa (SSA). We aimed to describe viral suppression among releasees at community follow up in Zambia, and examine the association between post-release substance use and viral suppression to identify actionable targets for a HIV transitional care pilot.
**Methods:** We prospectively enrolled incarcerated PLHIV at 5 correctional facilities in Zambia having the following eligibility criteria: ≥18 years old; release scheduled <30 days from screening; enrolled in the national HIV treatment program; and willing and able to provide voluntary informed consent and locator information. Study participants were recruited, screened, enrolled, and completed a baseline study visit pre-release, and then underwent one follow-up visit ~6 months post-release. Study visits included viral load (VL) testing and collection of clinical, socio-demographic, and psychosocial data. We calculated summary statistics for variables of interest and estimated the association between post-release substance use and VL suppression (<1,000 c/mL) using Cox proportional hazard modeling.
**Results:** From March 2017–December 2018, we screened 396 incarcerated people and enrolled 296 (75%) who met eligibility criteria. Of these, 267 (90%) had been on ART for ≥30 days and were included in the analysis. Of these, most were men (n=210, 79%), of median age 35 years (IQR:30–42), baseline CD4 of 390 (IQR:256–507), and 235 (88%) had viral suppression. 201 participants (75%) completed both follow-up VL testing and substance use screening at 7.3 months (IQR:5.3–10.5) post-release. Of these, 15 (7%) reported interval hazardous alcohol and/or drug use per the Alcohol/ Drug Use Disorders Identification Tests (AUDIT/ DUDIT), and 169 (84%) had VL suppression. Releasees with, versus those without, hazardous alcohol and/or drug use were 3.5 times (95% CI:1.4–9.0) as likely to have an unsuppressed VL post-release (Table).
**Conclusion:** In one of the first studies to prospectively follow justice-involved PLHIV in SSA, we observed a numerical decrease in the percent of participants with viral suppression post-release, and that female sex and hazardous alcohol and/or drug use were significantly associated with unsuppressed VL post-release. New transitional HIV care models are urgently needed in SSA to support HIV care engagement and address co-morbid substance use in this key population.

**Table:** Associations between characteristics of interest and unsuppressed viral load at a threshold of ≥1,000 copies/ml among 201 participants who completed both post-release viral load testing and substance use screening using validated tools.

| Characteristic | | % with Characteristic (n/N) | Unadjusted HR* (95% CI)^ | Adjusted HR* (95% CI)^ | p-value |
|---|---|---|---|---|---|
| **Sex** | Male | 79.1% (159/201) | 1 | 1 | 0.050 |
| | Female | 20.9% (42/201) | 1.94 (0.92, 4.09) | 2.16 (1.00, 4.65) | |
| **Age, years** | ≥40 | 32.3% (65/201) | 1 | 1 | 0.082 |
| | <40 | 67.7% (136/201) | 2.32 (0.89, 6.09) | 2.40 (0.90, 6.46) | |
| **Baseline CD4+ count** (cells/mm$^3$) | ≥200 | 86.6% (174/201) | 1 | 1 | 0.002 |
| | <200 | 13.4% (27/201) | 2.75 (1.22, 6.18) | 3.84 (1.64, 9.02) | |
| **Psychosocial support** (per the mMOS-SS)[@] | 21$^{st}$-100$^{th}$ percentile | 80.1% (161/201) | 1 | 1 | 0.531 |
| | <20$^{th}$ percentile | 19.9% (40/201) | 1.38 (0.62, 3.07) | 1.30 (0.57, 2.98) | |
| **Hazardous Alcohol and/or Drug use** (per the AUDIT/ DUDIT)[#] | No | 92.5% (186/201) | 1 | 1 | 0.008 |
| | Yes | 7.5% (15/201) | 2.62 (1.08, 6.36) | 3.53 (1.39, 8.98) | |

*HR: Hazard ratio; ^CI: 95% confidence interval; [@]modified Medical Outcomes Study Social Support Survey; [#]WHO Alcohol Use Disorder Identification Test (AUDIT)/ Drug Use Disorders Identification Test (DUDIT)

## 914 SUBSTANCE USE TREATMENT UTILIZATION AMONG WOMEN WITH AND AT RISK FOR HIV IN THE SOUTH

New Investigator Scholar

**Aditi Ramakrishnan**[1], Wendy A. Fujita[1], Cyra C. Mehta[1], Tracey Wilson[2], Steve Shoptaw[3], Adam W. Carrico[4], Adaora Adimora[5], Ellen F. Eaton[6], Mardge Cohen[7], Jennifer Cohen[8], Adebola Adedimeji[9], Michael Plankey[10], Deborah Jones Weiss[4], Aruna Chandran[11], Anandi N. Sheth[1]
*[1]Emory University, Atlanta, GA, USA, [2]SUNY Downstate Health Sciences University, Brooklyn, NY, USA, [3]Harbor–University of Los Angeles Medical Center, Torrance, CA, USA, [4]University of Miami, Miami, FL, USA, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]University of Alabama at Birmingham, Birmingham, AL, USA, [7]John H Stroger Jr Hospital of Cook County, Chicago, IL, USA, [8]University of California San Francisco, San Francisco, CA, USA, [9]Albert Einstein College of Medicine, Bronx, NY, USA, [10]Georgetown University, Washington, DC, USA, [11]The Johns Hopkins University, Baltimore, MD, USA*

**Background:** Substance use (SU) contributes to poor health outcomes among individuals with HIV and increases risk for HIV acquisition. The extent to which evidence-based interventions for SU management are utilized among women with HIV (WWH) and at risk for HIV (HIV-) is unknown. We sought to describe SU treatment utilization among WWH and HIV- women enrolled in the Southern sites of the Women's Interagency HIV Study (WIHS).
**Methods:** WWH and HIV- women who enrolled and followed in the WIHS in Atlanta, Birmingham/Jackson, Chapel Hill, and Miami with last observed visits from 2014-2020 were included. Current SU was defined as any non-medical use of drugs in the past year at last follow-up visit. SU treatment utilization was determined by self-reported use of medication replacement therapy or drug treatment program among women who reported current SU. Demographic, clinical, and sociobehavioral characteristics, including healthcare engagement, from the last visit were compared between women who did and did not report SU treatment.
**Results:** Among 870 women (625 WWH, 245 HIV-), 69% (n=603) reported SU in their lifetime (67% WWH, 75% HIV-), and 37% (n=320) reported current SU (36% WWH, 39% HIV-). Among women endorsing current SU, 82% reported marijuana use, 41% crack/cocaine, 4% opioids, 3% intravenous drugs, and 1% methamphetamine; the median age was 48.5 years, 81% identified as Non-Hispanic Black, 69% were unemployed, 87% had health insurance, 65% smoked cigarettes, 22% reported heavy drinking, and 43% endorsed depressive symptoms (Table). Only 11% (n=35) reported SU treatment in the last year (12% WWH, 9% HIV-). Among those reporting current SU, treatment utilization was endorsed among 50% reporting methamphetamine use, 30% intravenous drugs, 25% opioids, 20% crack/cocaine, and 7% marijuana. While healthcare visit attendance in the last 6 months did not significantly differ by SU treatment, the proportion of women attending a mental health visit in the last 6 months was higher among women who received treatment. Among WWH with current SU, retention in HIV care, viral suppression, and ART use did not significantly differ by SU treatment.
**Conclusion:** Despite high prevalence of current SU among women enrolled in the Southern WIHS sites, there was a substantial gap in SU treatment utilization across substance types, with only 1 in 10 overall reporting SU treatment. Further investigation of treatment underutilization is urgently needed to develop tailored implementation strategies for this population.

**Table.** Demographic, sociobehavioral, and clinical characteristics based on the last observed visit among Women's Interagency HIV Study (WIHS) participants enrolled in Southern US sites from 2014-2020 who reported substance use in the last year (n=320).

| Characteristics | Substance use treatment N=35, N (%) | No substance use treatment N=285, N (%) | p-value[1] |
|---|---|---|---|
| HIV serostatus | | | |
| HIV positive | 26 (74.2) | 199 (69.8) | 0.5856 |
| HIV negative | 9 (25.7) | 86 (30.2 ) | |
| Age, years, median (Q1, Q3) | 47 (38, 55) | 49 (38, 55) | 0.8929 |
| Race | | | |
| Non-Hispanic Black | 28 (80.0) | 232 (81.4) | 0.8409 |
| Else | 7 (20.0) | 53 (18.6) | |
| Health insurance | | | |
| No | 8 (22.9) | 34 (11.9) | 0.1056 |
| Yes | 27 (77.1) | 251 (88.1) | |
| Alcohol use[2] | | | |
| Abstain | 18 (51.4) | 91 (31.9) | 0.0532 |
| 0-7 drinks/week | 13 (37.1) | 128 (44.9) | |
| > 7 drinks/week[3] | 4 (11.4) | 66 (23.2) | |
| Cigarette smoking | | | |
| Never | 3 (8.6) | 47 (16.5) | 0.0220 |
| Former | 2 (5.7) | 60 (21.1) | |
| Current | 30 (85.7) | 178 (62.5) | |
| Depressive symptoms[4] | | | |
| No | 17 (48.6) | 162 (57.7) | 0.3067 |
| Yes | 18 (51.4) | 119 (42.4) | |
| Ever incarcerated | | | |
| No | 1 (2.9) | 94 (33.0) | 0.0002 |
| Yes | 34 (97.1) | 191 (67.0) | |
| Healthcare visit in last 6 months | | | |
| No | 6 (17.1) | 69 (24.2) | 0.3516 |
| Yes | 29 (82.9) | 216 (75.8) | |
| Mental health visit in last 6 months | | | |
| No | 13 (44.8) | 141 (65.3) | 0.0324 |
| Yes | 16 (55.2) | 75 (34.7) | |
| HIV care visit in last 6 months[4,5] | | | |
| No | 4 (17.4) | 55 (28.8) | 0.5803 |
| Yes | 19 (82.6) | 136 (71.2) | |
| HIV RNA <200c/mL[5] | | | |
| No | 14 (25.0) | 51 (28.0) | 0.2476 |
| Yes | 42 (75.0) | 131 (72.0) | |
| ART use[5] | | | |
| No | 1 (3.9) | 23 (11.6) | 0.3249 |
| Yes | 25 (96.2) | 176 (88.4) | |

[1] p-value from chi-square, t-test, or Fischer Exact test, where appropriate.
[2] Collected at first follow-up visit after enrollment.
[3] Heavy drinking defined as consuming more than 7 drinks per week.
[4] Defined as Center for Epidemiologic Studies-Depression score ≥ 16.
[5] Among women with HIV only.

## 915 RANDOMIZED TRIAL OF PATIENT ACTOR TRAINING TO IMPROVE PrEP SERVICES FOR AGYW IN KENYA

Late Breaking

**Pamela Kohler**[1], John Kinuthia[2], Anna Larsen[1], Felix Abuna[2], George Owiti[2], Joseph Sila[2], Tamara Owens[3], Valerie Kemunto[2], Harrison Lagat[2], Melissa Vera[1], Barbra A. Richardson[1], Jillian Pintye[1], Grace John-Stewart[1]
*[1]University of Washington, Seattle, WA, USA, [2]Kenyatta National Hospital, Nairobi, Kenya, [3]Howard University, Washington, DC, USA*

**Background:** Judgmental interactions, inaccurate information, and inadequate counseling from health providers negatively affects PrEP uptake. Strategies to improve quality of PrEP services for adolescent girls and young women (AGYW) are needed.

**Methods:** We conducted a cluster randomized trial of a standardized patient actor (SP) training intervention for PrEP providers to improve adherence to national guidelines and communication skills when offering PrEP to AGYW in Kenya. Twelve of 24 health facilities were randomized to receive SP training. All PrEP providers at intervention facilities (up to ten per site) participated in a 2-day training in adolescent health, national PrEP guidelines, values clarification, and communication skills, followed by role-playing and de-briefing with trained actors. SP scenarios of AGYW seeking PrEP were developed through qualitative interviews with AGYW. Control facilities received standard national training. The primary outcome was quality of care, assessed during routine visits at baseline and post-intervention, by "mystery shopper" unannounced SPs (USPs) blinded to intervention arm. Quality was measured in two domains: adherence to guidelines (yes/no) and communication skills (Likert scale). Intent to treat analysis compared post-intervention quality scores by randomization arm, clustering on facility and USP, and adjusting for baseline scores.

**Results:** Overall, 232 providers consented to USP visits, and 94 providers at intervention sites completed the training. Participants were a median age of 31 years, 58% female; 49% were nurses, 45% clinical officers, and 7% other counselors. Following SP training, USPs posed as AGYW seeking PrEP at facilities in 142 encounters (71 at intervention sites and 71 control sites; 5-6 encounters per site). The mean quality score was 73.6% at intervention sites and 58.4% at control sites [adjusted mean difference=15.3, 95% Confidence interval (CI): 9.4-21.1, p<0.001]. By domain, mean adherence to PrEP guidelines scores were 57.2% at intervention sites and 36.2% at control sites (adjusted mean difference=20.9, 95% CI: 12.5-29.4, p<0.001), and mean communications scores were 90.0% at intervention sites and 80.5% at control sites (adjusted mean difference=9.5, 95% CI: 5.5-13.6, p<0.001).

**Conclusion:** SP training significantly improved quality of care delivered by PrEP providers for AGYW in Kenya. Incorporating SP training and unannounced SP evaluation could potentially improve PrEP uptake among AGYW.

**Table 1. Intention-to-treat analysis: Effect of PrIYA-SP intervention on quality of PrEP counseling for AGYW**

| Outcome | Intervention sites N=12 Mean (Standard deviation [SD]) | Control sites N=12 Mean (SD) | Mean difference 95% Confidence Interval [CI], p-value | Adjusted Mean difference 95% CI, p-value |
|---|---|---|---|---|
| Overall quality | 73.6 (16.3) | 58.4 (16.7) | 15.2, 9.1-21.4, p<0.001 | 15.3, 9.4-21.1, p<0.001 |
| Domains | | | | |
| PrEP guideline adherence | 57.2 (25.4) | 36.2 (26.9) | 20.9, 12.2-29.7, p<0.001 | 20.9, 12.5-29.4, p<0.001 |
| Provider communication | 90.0 (10.9) | 80.5 (11.4) | 9.5, 5.1-13.9, p<0.001 | 9.5, 5.5-13.6, p<0.001 |

## 916 PROJECTED IMPACT OF EXPANDED LONG-ACTING INJECTABLE PrEP USE ON LOCAL HIV EPIDEMICS

**Ruchita Balasubramanian**[1], Parastu Kasaie[1], Melissa Schnure[1], David Dowdy[1], Maunank Shah[2], Anthony T. Fojo[2]
*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

**Background:** The Ending the HIV Epidemic (EHE) initiative aims to reduce HIV incidence in the US by 90% over a decade. Pre-exposure prophylaxis (PrEP) is a key component in this effort. Long-acting injectable (LAI) PrEP reduces the risk of HIV acquisition more than oral PrEP but its potential to impact local HIV epidemics remains unclear.

**Methods:** The Johns Hopkins HIV Economic Epidemiological model (JHEEM) is a dynamic model of HIV transmission in 32 high priority urban areas in the US. We leveraged JHEEM to project the incidence of HIV among men who have sex with men (MSM) from 2020-2030 under a range of interventions aimed at increasing PrEP use. In each of the 32 cities, we ran 1000 simulations testing an expansion of PrEP uptake to 10% above baseline levels of oral PrEP (either all oral PrEP, all LAI PrEP, or 50% oral + 50% LAI) as well as an expansion to 25% above baseline (all oral, all LAI, or 50% oral + 50% LAI). Interventions began in 2023 and scaled up over five years (fully implemented in 2027). Across simulations, we varied the efficacy and rates of discontinuation of oral PrEP and relative efficacy of LAI vs oral PrEP according to published estimates. We allowed the rates of discontinuation of LAI PrEP to range from 25-100% of the rate of oral PrEP discontinuation.

**Results:** In the absence of any intervention, baseline-levels of oral PrEP uptake ranged from 6% in Sacramento to 25% in New York in 2020. This led to a projected reduction in HIV incidence of 19% (95% Credible Interval [CrI] 1-36%) among MSM from 2020-2030 across all 32 cities. At 10% additional PrEP uptake, the reduction in incidence across all 32 cities ranged from 33% (95% CrI 18-47%) with all oral PrEP to 37% (95% CrI 23-50%) with all LAI PrEP. At 25% additional uptake, incidence reductions ranged from 50% (95% CrI 38-60% - all oral) to 55% (95% CrI 45-65% - all LAI). There was substantial variation between cities (see Table): at 25% uptake (50/50 oral, LAI), reductions in incidence ranged from 38% in Atlanta to 67% in Seattle.

**Conclusion:** The greatest potential impact of LAI PrEP is in expansion of total PrEP uptake in conjunction with oral PrEP. If availability of LAI PrEP can increase overall PrEP uptake by 25%, substantial reductions in HIV incidence can be achieved in key populations at the local level within 10 years. Nevertheless, availability of LAI PrEP alone without improvements in the HIV continuum of care is unlikely achieve reductions in line with EHE goals.

**Table. Reduction in Incidence of HIV from 2020-2030 Across Different Uptake Levels of Oral and Injectable PrEP within US Cities**

| | No Intervention | 10% Additional PrEP Uptake | | | 25% Additional PrEP Uptake | | |
|---|---|---|---|---|---|---|---|
| | | All Oral | Half Oral + Half LAI | All LAI | All Oral | Half Oral + Half LAI | All LAI |
| Atlanta | 9% | 20% | 22% | 23% | 34% | 38% | 40% |
| Austin | 34% | 47% | 50% | 51% | 62% | 65% | 67% |
| New York | 27% | 39% | 42% | 43% | 54% | 58% | 60% |
| Sacramento | 2% | 23% | 26% | 28% | 49% | 53% | 56% |
| San Francisco | 35% | 48% | 50% | 51% | 62% | 65% | 67% |
| Seattle | 15% | 40% | 44% | 47% | 63% | 67% | 70% |
| Total | 19% | 33% | 36% | 37% | 50% | 53% | 55% |

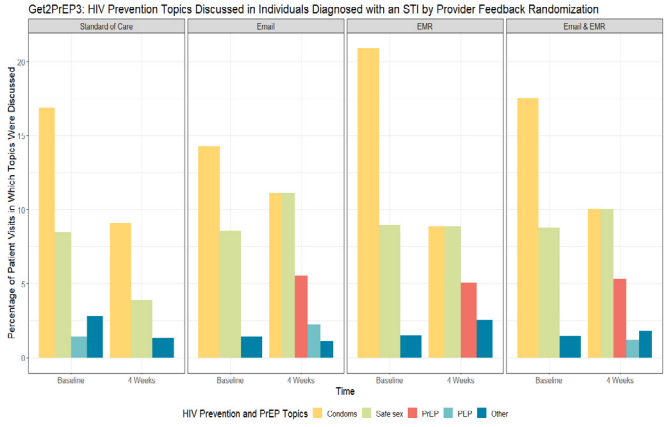
We report the reduction in HIV incidence among MSM from 2020 to 2030 under each intervention of varying PrEP uptake (10% or 25% uptake above baseline levels of oral PrEP of either all oral PrEP, all LAI PrEP, or 50% oral + 50% LAI). We report mean reduction over 1,000 simulations for 6 representative cities in the US as well as the total across 32 cities.

## 917 GET2PrEP3: RCT OF PROVIDER MESSAGING TO IMPROVE LINKAGE TO HIV PREVENTION SERVICES

**Jason Zucker**[1], Deborah A. Theodore[1], Caroline Carnevale[2], Eshiemomoh Osilama[1], Norman Archer[1], Lily Bonadonna[1], Elena Wadden[1], Nicholas Morley[1],

Simian Huang[1], Kathrine Meyers[3], Alwyn Cohall[1], Peter Gordon[1], Delivette Castor[1], Magdalena E. Sobieszczyk[1]
*[1]Columbia University Medical Center, New York, NY, USA, [2]New York Presbyterian Hospital, New York, NY, USA, [3]Aaron Diamond AIDS Research Center, New York, NY, USA*

**Background:** Pre-exposure prophylaxis (PrEP) effectively reduces HIV acquisition; however, achieving the full benefit of this intervention requires linking patients with PrEP providers, uptake, and effective use. Bacterial sexually transmitted infections (STIs) are biomarkers for HIV risk that can identify possible PrEP candidates. At our institution, one study revealed that PrEP was discussed with fewer than 5% of patients diagnosed with a bacterial STI; a follow-up study showed that adding an electronic medical record (EMR) lab comment prompting HIV prevention services that was added to all positive STI results did not increase the frequency of PrEP discussions.
**Methods:** We conducted a three-arm randomized controlled trial where patient visits with a positive STI test were randomized to receiving a personalized email message highlighting the patient's recent STI, PrEP candidacy, and local PrEP resources, including an email and phone number for referrals to the provider (arm 1); receiving the same information through an EMR message (arm 2), or no message (arm 3). The primary outcome was the provider's documented PrEP-discussion or referral four weeks after STI diagnosis. All patient-provider visits in which the patient tested positive for an STI were randomized. Visits were excluded if testing was performed in experienced sexual health settings, if PrEP had been discussed with the patient in the past 12 months, or if there was a contraindication to PrEP (eg, living with HIV).
**Results:** There were 191 unique visits randomized to the standard of care (N=66), email (N=65), and EMR messaging (N=60). The majority of patients were 14-24 years old (52%), women (78%), Hispanic ethnicity (62%), Black/African American (18%), and diagnosed in the outpatient setting (50%) or the emergency department (48%). Exactly 147 patients were positive for chlamydia, 31 for gonorrhea, and 16 for syphilis. 34% were symptomatic; 56% were tested as routine screening or by request. Patients whose provider received any message were 7% (CI 1.01-1.14) more likely to have a PrEP discussion or referral documented.
**Conclusion:** In a population of patients testing positive for an STI, personalized messaging to providers (by email or by EMR) increased PrEP discussions with potential PrEP candidates at one month. Future studies are needed to understand how to further optimize PrEP offers for those at highest risk in non-dedicated sexual healthcare settings.




## 918 PrEP RATHER THAN COVID-19 INFLUENCED SEXUAL ACTIVITY AMONG MSM IN TOKYO

**Daisuke Mizushima**[1], Misao Takano[1], Yasuaki Yanagawa[1], Takahiro Aoki[1], Koji Watanabe[1], Shinichi Oka[1]
*[1]National Center for Global Health and Medicine, Tokyo, Japan*

**Background:** COVID-19 drastically changed life style in Japan. However, the influence of COVID-19 on sexual activity among men who have sex with men (MSM) have not been fully understood. Although, the number of new HIV infection in Japan in 2020 decreased by 11.4%, the number of public HIV and sexually transmitted infection (STI) tests at health centers decreased by half due to overwhelmed burden by COVID-19, which made it difficult to access concise situations. Thus, we retrospectively evaluated incidence of HIV/STIs among MSM in Japan before and after COVID-19 endemic in a non HIV-infected MSM cohort in Tokyo, Japan.
**Methods:** MSM over 16 years old have been recruited in the cohort at Sexual Health Clinic in Tokyo, Japan since 2017. The participants were examined for HIV infection, syphilis (quantitative RPR/TPHA), and rectal/pharyngeal Chlamydia trachomatis and Neisseria gonorrhea infections every 3 months in the cohort. In the participants of the cohort, incidence of HIV and STI were evaluated before and after COVID-19 pandemic. The period between July 2018 and December 2019 was defined as before COVID-19 (BC) and the period between January 2020 and June 2021 was defined as after COVID-19 (AC). As other factors to influence on sexual activity, use of pre-exposure prophylaxis (PrEP) was also evaluated before and after COVID-19 pandemic.
**Results:** 1614 MSM were recruited in the cohort as of June 2021 (348 prior to June 2019, 661 in BC and 605 in AC). 21 (3.2%) and 14 (2.3%) MSM were excluded from the cohort due to HIV infection at the enrollment in BC and AC. The number and average age of MSM with at least 2 HIV/STI tests were 935 (34.4 years) in BC and 1324 (34.9 years) in AC, respectively. The table demonstrated that while the incidence of STIs showed no substantial changes from BC to AC in all MSM, the incidence of STIs decreased in the non-PrEP users and increased in the PrEP users consistently from BC to AC. The differences in the incidence of STIs between the non-PrEP and the PrEP users were more remarkable in AC than BC. In AC, the incidence of STIs almost tripled in the PrEP users compared to the non-PrEP users. These findings might be explained that increasing recognition of PrEP rather than the impact of COVID-19 leads to initiation of PrEP by MSM with higher risk in addition to risk compensation in the cohort.
**Conclusion:** PrEP should be implemented with intensive STI tests in Japan for further decrease in STIs in the long run.

| Incidence | Total | Non PrEP users | PrEP users |
|---|---|---|---|
| Before COVID-19 (2018/7-2019/12) (FU person-year / n) | 587.9 PY / 727 | 358.2 PY / 500 | 229.6 PY / 227 |
| HIV | 2.6 %/year / 15 | 4.2 %/year / 15 | 0 %/year / 0 |
| Syphilis | 4.6 %/year / 27 | 4.2 %/year / 15 | 5.2 %/year / 12 |
| Chlamydia | 24.7 %/year / 145 | 22.3 %/year / 80 | 28.3 %/year / 65 |
| Gonorrhea | 16.7 %/year / 98 | 17.6 %/year / 63 | 15.2 %/year / 35 |
| After COVID-19 (2020/1-2021/6) (FU person-year / n) | 964.2 PY / 1082 | 662.8 PY / 721 | 301.4 PY / 361 |
| HIV | 1.2 %/year / 12 | 1.8 %/year / 12 | 0 %/year / 0 |
| Syphilis | 4.8 %/year / 46 | 2.9 %/year / 19 | 9.0 %/year / 27 |
| Chlamydia | 32.0 %/year / 309 | 19.9 %/year / 132 | 58.7 %/year / 177 |
| Gonorrhea | 14.7 %/year / 142 | 10.0 %/year / 66 | 25.2 %/year / 76 |

PrEP: Pre exposure prophylaxis, COVID: coronavirus disease, FU: follow up, PY: person year

## 919 SEXUAL HEALTHCARE USE, PrEP USE, AND THE INCIDENCE OF STI AMONG MSM DURING COVID-19

New Investigator Scholar

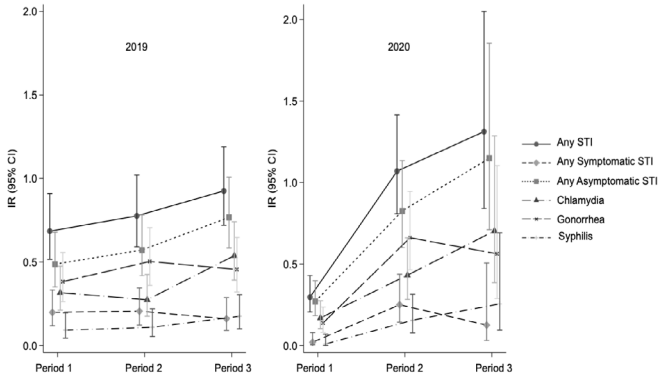
**Feline De IL Court**[1], Anders Boyd[1], Liza Coyer[1], Mark van den Elshout[1], Henry J. de Vries[1], Amy Matser[1], Elske Hoornenborg[1], Maria Prins[1]
*[1]Public Health Service Amsterdam, Amsterdam, Netherlands*

**Background:** This study explores the effects of COVID-19 restrictions on sexual healthcare use, pre-exposure prophylaxis (PrEP) use, and sexually transmitted infection (STI) incidence among men who have sex with men (MSM) participating in a PrEP demonstration project in Amsterdam, the Netherlands (AMPrEP).
**Methods:** We retrieved data from 2019-2020 for AMPrEP participants with ≥1 study visit in 2019 (n=305), and two questionnaires on COVID-19 measures and sexual behaviour in 2020 and 2021 (n=203; n=160). Analyses were stratified for three periods of COVID-19 restrictions (first: 15/3/2020-15/6/2020; second: 16/6/2020-15/9/2020; third: 16/9/2020-31/12/2020 or 1/4/2021 for COVID-19 questionnaire data). Evaluated endpoints included proportion returning for sexual healthcare during COVID-19, change in PrEP use (increased/unchanged vs. deceased/stopped; relative to 2019), and incidence of any STI (chlamydia, gonorrhoea, or syphilis; diagnosed at clinic/study visit) or HIV. We modelled determinants of care and PrEP use via multivariable logistic regression, and STI incidence using piecewise Poisson regression; comparing 2020 periods to those in 2019.
**Results:** Of the 305 included in the analysis, 72.8% (n=222) of participants returned for care during COVID-19, among which 147, 190, and 148 visits took place during the first, second, and third period of COVID-19 restrictions, respectively. Daily (versus event-driven) PrEP use was significantly associated

with returning for care across periods (p<0.001). Increased/unchanged PrEP use was reported by 55.2% (n=112), 58.1% (n=93), and 55.6% (n=89) during the first, second, and third periods, respectively. Increased/unchanged PrEP use was more likely among those reporting chemsex in the first (p=0.001) and third (p=0.020) periods, and those reporting increased/unchanged number of sex partners relative to 2019 during the second period (p=0.010). STI incidence was significantly lower in 2020 than 2019 during the first (IRR=0.43, 95%CI=0.28-0.68), yet seemed higher during the second (IRR=1.38, 95%CI=0.95-2.00) and third periods (IRR=1.42, 95%CI=0.86-2.33), albeit non-significantly (figure 1). No new HIV infections were diagnosed.

**Conclusion:** COVID-19 restrictions coincided with reduced care and PrEP use. The significantly lower STI incidence during the first period of COVID-19 restrictions and subsequent increase suggests a delayed diagnosis effect. We need ways to ensure continued access to sexual healthcare during restrictions.

**Figure 1:** *STI incidence in 2019 and 2020 among AMPrEP participants, both stratified for the three periods of COVID-19 restrictions imposed in 2020 in the Netherlands*




Explanation of data: IR = incidence rate per person-year; 95% CI = 95% confidence interval. Explanation of periods of COVID-19 restriction in the Netherlands, applied to both 2019 and 2020 data: first=15/3/2020-15/6/2020 including a nationwide lockdown; second=16/6/2020-15/9/2020 including few public restrictions while social distancing remained; third=16/9/2020-31/12/2020 including partial lockdown with restricted access to public spaces and curfew. Any STI refers to any chlamydia, gonorrhoea, or syphilis diagnosis at a study or clinic visit. Any symptomatic STI refers to any chlamydia, gonorrhoea, or syphilis diagnosis at a study or clinic visit for which symptoms were reported by the patient. Any asymptomatic STI refers to any chlamydia, gonorrhoea, or syphilis diagnosis at a study or clinic visit for which no symptoms were reported by the patient.

## 920 ACCEPTABILITY AND ELIGIBILITY FOR PrEP AMONG MEDICAL MALE CIRCUMCISION CLIENTS

**Tendesayi Kufa-Chakezha**[1], Ocean Tobaiwa[2], Sean M. Patrick[3], Khumbulani Moyo[4], Phil Dorrell[2], Nichola Lutchman[5], Erushka Pillay[2], Adrian Puren[1]
*[1]National Institute for Communicable Diseases, Johannesburg, South Africa, [2]Clinton Health Access Initiative, Pretoria, South Africa, [3]University of Pretoria, Pretoria, South Africa, [4]Right to Care, Johannesburg, South Africa, [5]Gauteng Department of Health, Johannesburg, South Africa*

**Background:** Integration of voluntary male medical circumcision services (VMMC) with other HIV prevention interventions may increase access to combination HIV prevention among males. We describe pre-exposure prophylaxis (PrEP) acceptability and eligibility among adult males attending VMMC services in Gauteng Province South Africa.

**Methods:** Cross-sectional study conducted during the period June - October 2021at six public sector facilities offering VMMC services in two districts of Gauteng Province in South Africa. Eligible males 18 years or older were enrolled into the study. Interviewer-administered questionnaires with questions on PrEP knowledge, willingness to use PrEP (six item Likert scale each item rated 1- 5 corresponding to strongly disagree- strongly agree), willingness to pay for it and eligibility based on national guidelines were used to collect data. Rapid HIV testing was offered. HIV negative participants who were syphilis serology positive at enrolment, had ≥ two sexual partners in the preceding12 months or those reported self-perceived risk of HIV infection were considered PrEP eligible. PrEP knowledge, acceptability and eligibility were determined as proportions of those enrolled.

**Results:** Of 612 males enrolled, 505 (82.5%) were HIV negative and included in the analysis. The median age of those included was 31.5 years (IQR 25.1-37.4years) with 154 (30.9%) married or living as married, 181 (36.4%) employed, 120 (23.8%) reporting one or non-regular sexual partners in the preceding three months, with close to half [238/505 (47.5%)] not having heard of PrEP. The median total score on the Likert scale for willingness to use PrEP was 25 (IQR 22- 27) out of a highest possible score of 30. Assuming that items rated 4 or 5 indicated high willingness to use PrEP as an HIV prevention method, 313 (68.3%) of the individuals who responded to all six questions (N=458) were willing to use PrEP. Willingness to use PrEP was highest for use at sex act and lowest for three times weekly dosing PrEP. Clients were willing to pay a median US$3.33 (US$ 1.33-US$6.67)/ month (1US$ = ZAR). One hundred and fifty one clients (29.9%) met criteria for PrEP eligibility and could be referred for access to or provided PrEP on site.

**Conclusion:** A large proportion of enrolled males attending VMMC services were not aware of PrEP but were willing to use with almost 30% eligible based on current criteria. Integrating PrEP with VMMC services maybe feasible and should be explored.

**Distribution of PrEP acceptability scores on Likert Scale (N= 505; Cronbach α= 0.81)**

| Item | N | Strongly disagree | Disagree | Neither agree or disagree | Agree | Strongly agree |
|---|---|---|---|---|---|---|
| If PrEP was available for the prevention of HIV infection, would you intend to use it as a HIV prevention method? | 498 | 35 (7.0) | 9 (1.8) | 7 (1.4) | 84 (16.9) | 363 (72.9) |
| If PrEP was available as an HIV prevention tool , would you use it daily | 490 | 58 (11.8) | 27 (5.5) | 18 (3.7) | 145 (29.0) | 242 (49.4) |
| If PrEP was available as an HIV prevention tool , would you use it three times a week | 475 | 67 (14.1) | 57 (12.0) | 101 (21.3) | 158 (33.3) | 92 (19.4) |
| If PrEP was available as an HIV prevention tool , would you use it once a week | 484 | 70 (14.5) | 73 (15.1) | 72 (14.9) | 145 (30.0) | 124 (25.6) |
| If PrEP was available as an HIV prevention tool , would you use it every time you had sex | 493 | 39 (7.9) | 18 (3.7) | 26 (5.3) | 97 (19.7) | 313 (63.5) |
| I am willing to pay for my PrEP in the future | 496 | 50 (10.1) | 41 (8.3) | 13 (2.6) | 123 (24.8) | 269 (54.2) |

## 921 HEALTH OF LONG-TERM PrEP USERS IN AUSTRALIA – FINDINGS FROM THE X-PLORE COHORT

**Vincent J. Cornelisse**[1], Dean Murphy[1], Michael Traeger[2], Mark Stoove[2], Brian Price[1], Edwina J. Wright[3]
*[1]Alfred Hospital, Melbourne, Australia, [2]Burnet Institute, Melbourne, Australia, [3]Monash University, Melbourne, Australia*

**Background:** Daily or on-demand HIV pre-exposure prophylaxis (PrEP) using TDF/FTC is highly effective in preventing HIV acquisition in gay men. Little is known about longer term physical and mental health outcomes among PrEP users. We report on PrEP use and physical and mental health outcomes in Australia's X-PLORE cohort, which follows PrEP users long term.

**Methods:** Over 5000 participants enrolled in PrEPX, an Australian PrEP demonstration study, between July 2016 and April 2018. In 2018, 1705 PrEPX participants enrolled into the X-PLORE cohort. Between 13 March and 31 May 2021, we administered an online survey of X-PLORE participants, focusing on ongoing PrEP use and self-reported physical and mental health. Current mental health was assessed using GAD-7 and PHQ-9 questionnaires for anxiety and depression, respectively.

**Results:** The survey was completed by 534 of 1705 (31%) X-PLORE participants, consisting mainly (99.8%) of cis-gender gay men, median age of 48 years (IQR 38–57). Median PrEP use duration was 48 months (IQR 36–56). Among the 75% of respondents who were using PrEP at survey completion, 86% were using it daily, 9% on-demand, and 5% a combination of these methods. Approximately half (54%) had ever interrupted their PrEP use, of whom 90% reported using other HIV risk reduction strategies during these periods. Since commencing PrEP, 343 (64%) reported being diagnosed with at least one bacterial STI, 19 (4%) with renal problems, 14 (3%) with bone fracture(s), 7 (1%) with osteopenia, 64 (12%) with depression, and 73 (14%) with anxiety. Median PHQ-9 score was 4 (IQR 1-8), and median GAD-7 score was 3 (IQR 0-7), respectively indicating no to minimal depression or anxiety for most respondents. An overwhelming majority (90%) rated their health as generally "good" to "excellent" and 23% reported improved health since starting PrEP, of whom 69% attributed this improvement to PrEP. 71% reported no change in health. 6% reported a deterioration in health since starting PrEP, but only 4 (1%) participants attributed this deterioration to PrEP, which they specified as gastrointestinal intolerance and more STIs.

**Conclusion:** 75% of survey respondents maintained PrEP use after a median of four years and reported good physical and mental health. This was also reflected in healthy scores on depression and anxiety scales. Many respondents reported improved health since starting PrEP, and they attributed this to PrEP.

## 922 DEFERRING CREATININE CLEARANCE TESTING TO SUPPORT PrEP UPTAKE IN YOUNG WOMEN

New Investigator Scholar

**Craig J. Heck**[1], Lara Lewis[2], Natasha Samsunder[2], Quarraisha Abdool Karim[2]
*[1]Columbia University, New York, NY, USA, [2]Centre for the AIDS Programme of Research in South Africa, Durban, South Africa*

**Background:** Young women (aged 15-24 years) in eastern and southern Africa have high HIV risk but low oral PrEP uptake. Confirmation of normal creatinine clearance levels (CrCl, ≥60 mL/min), a pre-requisite for oral PrEP initiation in many settings, reduces uptake of oral PrEP. Given the high rates of new HIV infections in young women and that oral PrEP is one of the few self-initiated prevention options available for young women, we measured the frequency of renal dysfunction pre- and post-PrEP initiation among young women in South Africa.

**Methods:** Data from an oral PrEP demonstration project undertaken between June 2017 and July 2018 in KwaZulu-Natal, South Africa, were used to assess the prevalence of renal dysfunction (<60 mL/min) using CrCl levels at project screening, as well as reasons for non-enrollment. Among PrEP users who had detectable drug levels, baseline renal function was compared with CrCl levels 3 months after PrEP initiation. Since the regulatory approval for the inclusion of 15- to 17-year-old women was delayed by almost a year, the data for this age group is exploratory.

**Results:** A total of 319 young women (n=295 aged 18-24 years, n=24 aged 15-17 years) were screened, and all displayed normal renal function at baseline (Table 1). Enrollment was high among screened individuals; however, of non-enrollees, 60.0% (48/82 aged 18-24 years, 6/8 aged 15-17 years) did not return for PrEP initiation, a potential proxy measure of lost motivation between CrCl measurement and PrEP initiation. Among enrollees with detectable drug levels at month 3 (n=31), CrCl reductions were modest. Between screening (mean: 158.3, range: 80.0 to 253.0) and month 3 (mean: 145.1, range: 77.0 to 206.0), mean CrCl levels decreased by 7.5% (range: -23.8% to 29.1%, p-value: 0.0013), a reduction that is within the normal range.

**Conclusion:** In this population of young women, renal dysfunction was rare, and short-term oral PrEP use did not lead to clinically significant CrCl reductions. Immediate PrEP initiation-with CrCl confirmation within a 30-day follow-up visit-appears to be a safe, streamlined option for enhancing PrEP uptake in this population.

**Table 1. Baseline CrCl levels of Young Women**

| | Aged 15-17 years (n=23)† | Aged 18-24 years (n=269)‡ | Aged 15-24 years (n=292)§ |
|---|---|---|---|
| **Mean CrCl levels (SD)** | 150.4 (42.6) | 155.4 (43.6) | 155.0 (43.6) |
| **Range** | 100.0 to 258.0 | 76.0 to 362.0 | 76.0 to 362.0 |

SD: Standard Deviation, CrCl: Creatinine Clearance
† 1 individual aged 15-17 years did not have CrCl data
‡ 26 individuals aged 18-24 did not have CrCl data
§ 27 individuals aged 15-24 did not have CrCl data

## 923 A COMPARISON OF SELF-REPORTED PrEP ADHERENCE AND OBJECTIVE MEASURES IN KENYA

New Investigator Scholar

**Ashley Bardon**[1], Kenneth Ngure[2], Peter A. Mogere[3], Dorothy Mangale[1], David Chege[3], Catherine Kiptinness[3], Stephen Gakuo[3], Sarah Mbaire[3], Peter Anderson[4], Nelly R. Mugo[1], Jared Baeten[1], Katrina Ortblad[1]
*[1]University of Washington, Seattle, WA, USA, [2]Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya, [3]Kenya Medical Research Institute, Nairobi, Kenya, [4]University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

**Background:** Objective adherence metrics for evaluating PrEP adherence are not widely available due to resource constraints; therefore, providers often rely on clients' self-reported behaviors to identify suboptimal adherence. Clinical trials have found that self-reported PrEP adherence commonly overestimates actual adherence, but little is known about the accuracy of self-reported adherence measures in implementation settings where clients desire PrEP. We aimed to estimate the accuracy of self-reported PrEP adherence among clients retained in care in Kenya.

**Methods:** We used data from participants enrolled in a randomized implementation trial (JiPime-JiPrEP, CT.gov: NCT03593629) evaluating six-month PrEP dispensing supported with interim HIV self-testing in Kenya. At six months, participants retained in care self-reported their PrEP adherence using five commonly-used items and provided a dried blood spot (DBS) sample for laboratory analyses. We measured tenofovir-diphosphate (TFV-DP) in the DBS samples via liquid chromatography/tandem mass spectrometry. Using multivariate logistic regression models; adjusting for age, risk group, and study arm; we estimated the adjusted odds ratios (aORs) of undetectable TFV-DP and <700 fmol/punch TFV-DP for each self-reported PrEP adherence measure.

**Results:** From December 2018 to September 2020, 398 participants returned for a six-month PrEP visit and provided a DBS sample. Among these, 26% (103/398) had no detectable TFV-DP, and 49% (194/398) had <700 fmol/punch TFV-DP. Most self-reports of poor PrEP adherence in the selected questions were significantly (p<0.05) associated with undetectable and <700 fmol/punch TFV-DP concentrations (Table 1). Self-reported fair, poor, or very poor PrEP adherence was most strongly associated with no detectable TFV-DP (aOR 11.8, 95% CI 5.5-25.2). Self-reported PrEP discontinuation was most strongly associated with <700 fmol/punch TFV-DP concentrations (aOR 37.6, 95% CI 4.8-294.4).

**Conclusion:** In this implementation setting in Kenya, PrEP participants had high adherence, and most self-reported poor adherence measures were associated with objective poor adherence. In the absence of objective PrEP adherence measures, a simple self-report of PrEP adherence ('How well have you taken PrEP since initiation?') and continuation ('Are you still taking your PrEP medication?') may be the most accurate measures of identifying clients' suboptimal PrEP adherence in Kenya, as compared to other commonly-used self-reported adherence metrics.

**Table 1. Adjusted odds ratios (aORs) of objective PrEP adherence levels for self-reported adherence measures among PrEP clients in Kenya**

| Self-Reported Adherence Measures | TFV-DP concentrations (fmol/punch) <BLQ[1] n (%) | ≥BLQ-699 n (%) | ≥700 n (%) | No TFV-DP detected[1] aOR[2] (95% CI) | p-value | TFV-DP concentration <700 fmol/punch aOR[2] (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| **Days since last PrEP dose was taken[3]** | | | | | | | |
| *0* | 10 (3%) | 6 (2%) | 27 (7%) | *REF* | -- | *REF* | -- |
| *1* | 46 (12%) | 59 (15%) | 168 (42%) | 0.6 (0.3 – 1.5) | 0.28 | 1.0 (0.5 – 2.1) | 0.99 |
| *>1* | 47 (12%) | 25 (6%) | 9 (2%) | 5.1 (2.0 – 12.7) | <0.01 | 16.4 (6.0 – 44.8) | <0.01 |
| **Are you still taking your PrEP medication?[3]** | | | | | | | |
| *Yes* | 84 (21%) | 84 (21%) | 203 (51%) | *REF* | -- | *REF* | -- |
| *No* | 18 (5%) | 7 (2%) | 1 (0%) | 10.0 (3.8 – 26.4) | <0.01 | 37.6 (4.8 – 294.4) | <0.01 |
| **Number of days missed taking PrEP in the past month** | | | | | | | |
| *0-8* | 58 (15%) | 70 (18%) | 196 (49%) | *REF* | -- | *REF* | -- |
| *9-16* | 7 (2%) | 5 (1%) | 4 (1%) | 2.3 (0.7 – 6.9) | 0.15 | 3.0 (0.9 – 10.5) | 0.08 |
| *17-30* | 38 (10%) | 16 (4%) | 4 (1%) | 10.0 (5.0 – 19.8) | <0.01 | 23.2 (7.8 – 68.4) | <0.01 |
| **How well have you taken PrEP since initiation?[3]** | | | | | | | |
| *Excellent, very good, or good* | 69 (17%) | 79 (20%) | 202 (51%) | *REF* | -- | *REF* | -- |
| *Fair, poor, or very poor* | 33 (8%) | 12 (3%) | 2 (1%) | 11.8 (5.5 – 25.2) | <0.01 | 36.3 (8.3 – 158.1) | <0.01 |
| **In general, how often do you take PrEP?[3]** | | | | | | | |
| *All of the time, most of the time, or a good bit of the time* | 71 (18%) | 81 (20%) | 200 (50%) | *REF* | -- | *REF* | -- |
| *Some of the time, a little bit of the time, or none of the time* | 31 (8%) | 10 (3%) | 4 (1%) | 11.1 (5.1 – 24.1) | <0.01 | 15.7 (5.2 – 47.2) | <0.01 |

*aOR=adjusted odds ratio, BLQ=below the limit of quantification CI=confidence interval, FTC-TP=emtricitabine-triphosphate, PrEP=pre-exposure prophylaxis, TFV-DP=tenofovir-diphosphate*
[1] *Below the limit of quantification (<31.3 fmol/punch)*
[2] *Adjusted for study arm, study population (men in serodifferent couple, women in serodifferent couple, singly-enrolled women), and age group (<34 years, ≥34 years)*
[3] *Missing for 1 participant*

## 924 PrEP ROLLOUT AND COVID-19 ARE IMPACTING COMMUNITY-BASED TESTING FOR HIV & OTHER STIs

**Christoph Boesecke**[1], Torben Kimhofer[2], Christopher Tocha[3], Oliver Schubert[3], Rainer Rybak[3], Klaus Kuhlen[3], Christoph Klaes[3], Jürgen K. Rockstroh[1]
*[1]Bonn University Hospital, Bonn, Germany, [2]Murdoch University, Murdoch, Australia, [3]AIDS-Hilfe Köln, Cologne, Germany*

**Background:** Published clinical and epidemiological data on individuals undergoing anonymous testing for sexually transmitted diseases (STI) in Germany are sparse. Here we report annual results of STI screenings and survey data from a large community based STI testing Checkpoint in Cologne, Germany in light of increased PrEP roll-out and the COVID-19 pandemic.

**Methods:** From January 2017 to December 2020, data on STI screening, clinical, demographic, sexual information was anonymously recorded for individuals attending the Checkpoint in Cologne. Visitors were screened for HIV, syphilis, chlamydia, gonorrhea and hepatitis C using point of care testing kits. Positive tests were validated.

**Results:** Overall, screening was performed on 15,153 visitors aged 16 to 85 years. Three main reasons were identified: recent HIV risk situation (40%), routine testing (23%), new relationship (21%). The largest visitor group represented MSM with a mean frequency of 40% across all years, followed by MSW (28%) and WSM (22%). Annual visitor numbers increased from 3,838 in 2017 by +3% and +6% for years 2018 and 2019, respectively. However, these figures declined by 40% in 2020 (COVID-19 lockdown). Frequency of MSM visitors declined from 46% in 2017 to 42%, 38%, and 35% in 2018 to 2020, respectively. In contrast, visitor numbers increased for all other groups from 2017 to 2020, with the highest relative change observed for WSW (+94%), followed by MSW (+25%) and MSW (+16%). Annual number of visitors screened for HIV declined from 55% in 2017 to 42% in 2020, with increasing test frequencies for chlamydia and gonorrhoea (17% in 2017 to 29% in 2020) and for HCV (4% in 2017 to 9% in 2020). Syphilis screening frequency remained constant at approximately 19% annually. MSM had the highest disease frequency but MSW and WSM showed a continuous increase in chlamydia infections from 2017 to 2020 (from 20% to 30% and 13% to 22%, respectively). Number of MSM visitors on PrEP increased from 2017 onwards, with +46% and +52% for years 2018 and 2019, and 7% for 2020 (COVID-19 lockdown).

**Conclusion:** Checkpoint was able to detect relevant STIs in 5% of all visitors thereby underling the importance of community-based testing sites particularly with increased PrEP roll-out and despite COVID-19 lockdown restrictions. Still, MSM remain at highest risk for contracting HIV highlighting the continuous need for educational activities as well as low-threshold and cost-free STI screening capacities.

### 925 PrEP DISCONTINUATION AMONG WOMEN IN US COMMUNITY HEALTH CENTERS

**Whitney Irie**[1], Jonathan Todd[2], Kenneth H. Mayer[3], Elvin H. Geng[4], Douglas Krakower[5], Julia Marcus[1]

*[1]Harvard Medical School, Boston, MA, USA, [2]OCHIN, Inc., Portland, OR, USA, [3]The Fenway Institute, Boston, MA, USA, [4]Washington University in St Louis, St Louis, MO, USA, [5]Beth Israel Deaconess Medical Center, Boston, MA, USA*

**Background:** Of the estimated 176,670 U.S. cisgender women with indications for HIV preexposure prophylaxis (PrEP), less than 10% used it in 2019, and women who initiate PrEP have higher rates of discontinuation compared with men. Large observational studies are needed to identify factors associated with PrEP discontinuation among women, particularly in safety-net settings that serve women at disproportionately high risk of HIV infection.

**Methods:** We conducted an observational cohort study of adult cisgender women prescribed PrEP during 2012–2019 in a national network of community health centers (OCHIN; 83% uninsured or publicly insured and 67% below the federal poverty line [FPL]). Clinical and sociodemographic data were extracted from electronic health records. We evaluated the one-year cumulative incidence of discontinuation, defined as 60 days without medication based on dates of prescriptions, and used unadjusted Cox regression models to identify factors associated with discontinuation.

**Results:** Of 9741 people prescribed PrEP, 644 (7%) were cisgender women and included in the study population. Mean age was 36 years; 40% were non-Hispanic White, 31% were non-Hispanic Black, and 20% were Latina. Most were on Medicaid (45%), uninsured (27%), or on other public health insurance (3%); 74% had incomes below the FPL. Among women prescribed PrEP, the cumulative incidence of discontinuation within one year was 78% (95% CI: 74%–81%). The risk of discontinuation was higher among women who were on Medicaid (unadjusted hazard ratio [HR] 1.5, 95% CI: 1.2–2.0), uninsured (HR 2.3, 95% CI: 1.8–3.1), or on other public insurance (HR 2.3, 95% CI: 1.4–3.9) compared with those on private insurance; among women with incomes <100% of the FPL (HR 2.1, 95% CI: 1.4–3.0) or 100-200% of the FPL (HR 1.7, 95% CI: 1.1–2.5) compared with those with incomes >200% of the FPL; and among women in the South compared with those in the Midwest/Northeast (HR 1.4, 95% CI: 1.1–1.8). Race, ethnicity, and age were not associated with discontinuation.

**Conclusion:** Cisgender women account for 18% of new HIV infections in the U.S. but only 7% of people prescribed PrEP at community health centers. Among women prescribed PrEP, more than 3 in 4 discontinue within one year, and risk of discontinuation is higher among women who are underinsured, lower-income, or living in Southern states. Policy changes and novel implementation strategies are needed to ensure easy access to PrEP for women, particularly those with structural barriers to care.

### 926 USING SAFE SPACE MODEL TO SCALE UP HIV PREVENTION IN ADOLESCENT GIRLS AND YOUNG WOMEN

**Andrew W. Wafula**[1], Philip Masaulo[1], Jane Thiomi[1], Benard Ogony[1], Peris M. Nasimiyu[1], Paul Musingila[2], Carol Kambona[2]

*[1]LVCT Health, Nairobi, Kenya, [2]US Centers for Disease Control and Prevention Kisumu, Kisumu, Kenya*

**Background:** HIV prevalence in 15-64-year-olds in Migori County remains high at 13%, nearly 2.7 times higher than the national prevalence (4.9%) and 28% of all new HIV infections were among adolescent 10-19 years, while 52% were young people age 15-24 years. LVCT Health STEPS project implemented the Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) program in 12 wards in Migori County with a goal of reducing new HIV infections among adolescent girls and young women (AGYW) aged 10-24 years. A combination of evidence-based behavioral, structural, and biomedical interventions were delivered through the safe space (SS) model.

**Methods:** The DREAMS program mobilized, screened for HIV vulnerability, enrolled and offered services to eligible AGYW between June 2017 and June 2021. Mentors, facilitators, and health service providers were trained and engaged to provide mandatory primary and need-based secondary interventions in community spaces considered to be safe from harassment, where AGYW could have fun, relax, display talents, and express themselves. AGYW were segmented based on age categories, geographic location, marital, and schooling status. Due to COVID-19 pandemic, AGYW participation was reduced from 30 to 15 and SS held in open spaces while observing ministry of health protocols. Service completion data was uploaded in DREAMS database, exported, and analysed in Excel.

**Results:** By June 2021, 1,206 SS were established. A total of 52,477 AGYW were screened for vulnerability and 93% (47,587) enrolled in DREAMS. Majority, 83% (39,603) were active at SS and received primary age-based interventions including: 96% (38,064) gender-based violence (GBV) screening, 98% (38,960) financial literacy training, 97% (38,283) school/community-based HIV and violence prevention intervention. Of the 30,759 AGYW eligible for HIV testing services (HTS), 95% received HTS, 98% (30,067) PrEP education, 99% (30,356) contraceptive method mix education, 99% (30,318) condom education and 79% (9,388) received entrepreneurship training. AGYW were prioritized for secondary interventions. Of 2,339 eligible for PrEP, 89% were initiated, among 5,097 sexually active, 99% received contraceptives. Additionally, 92% (17,778) were supported on education subsidy and 60% (7,718) on economic strengthening, and of those disclosing GBV, 100% (16,560) received post violence care.

**Conclusion:** Safe spaces are platforms for scaling up comprehensive HIV prevention interventions among AGYW.

### 927 HIGH PrEP UPTAKE AND LOW HIV VIREMIA WHEN PrEP IS INTEGRATED INTO UGANDAN ART CLINICS

**Renee Heffron**[1], Timothy Muwonge[2], Dorothy Thomas[1], Florence Nambi[3], Lylianne Nakabugo[3], Joseph Kibuuka[3], Erika L. Feutz[1], Allison A. Meisner[4], Katherine K. Thomas[1], Norma Ware[5], Jane A. Simoni[1], Ingrid T. Katz[6], Herbert Kadama[7], Andrew Mujugira[2]

*[1]University of Washington, Seattle, WA, USA, [2]Infectious Diseases Institute, Kampala, Uganda, [3]Infectious Disease Institute, Kampala, Uganda, [4]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [5]Harvard University, Cambridge, MA, USA, [6]Brigham and Women's Hospital, Boston, MA, USA, [7]Ministry of Health Uganda, Kampala, Uganda*

**Background:** Global scale-up of HIV (pre-exposure prophylaxis) PrEP includes targeting HIV-negative people in serodifferent partnerships with people living with HIV. There are few data to describe whether there is any impact of integrating PrEP into an existing HIV program vis-à-vis HIV treatment outcomes.

**Methods:** Using a stepped wedge cluster randomized trial design, we launched PrEP delivery in Kampala, Uganda for HIV-negative members of serodifferent couples by integrating PrEP into existing HIV testing and ART programs for people living with HIV. The program provided PrEP training for ART clinic providers, ongoing technical assistance, a provisional PrEP supply chain mechanism, and routine reports enabling clinics to track success with PrEP provision. Primary data to monitor PrEP initiation, PrEP refills, ART initiation, and HIV viremia were collected through data abstraction of routine medical records from HIV serodifferent couples sequentially enrolling at the ART clinics. For participants with missing viral load data, medical records were reviewed and participants contacted to understand reasons for the missing data (eg, lost to follow up, clinic transfer, death, unknown), enabling imputation of viral suppression. Modified Poisson regression models, controlling for time and cluster, compared viral suppression (<1000 copies/ml) before and after launching PrEP delivery.

**Results:** From June 2018-December 2020, we enrolled 1,381 HIV serodifferent couples into the Partners PrEP Program at 12 ART clinics in public health facilities in Kampala and Wakiso, Uganda, including 730 enrolled prior to and 651 after the launch of PrEP delivery. Participants' demographic characteristics were similar across facility groupings and trial steps, including median age of 28 (IQR 23-34) and the female was the partner living with HIV in 62% of couples. Among HIV-negative partners enrolled after PrEP launch in their clinic, 81% (527/651) initiated PrEP within 90 days of enrolling, 42% received a refill one month later, and 11% sought a refill 6 months later. Of partners living with HIV, 99% initiated ART within 90 days of enrollment. Of people enrolled during control and intervention periods, 81.9% and 76.7% were virally suppressed (RR=0.94, 95% CI: 0.82-1.07), a stable finding in multiple sensitivity analyses.

**Conclusion:** Integration of PrEP delivery into ART clinics reached a high proportion of people in HIV serodifferent relationships with no substantial impact on ART use by partners living with HIV.

**928 PHARMACY-BASED PrEP INITIATION AND CONTINUATION IN KENYA: FINDINGS FROM A PILOT STUDY**

**Katrina Ortblad**[1], Peter A. Mogere[2], Victor Omollo[3], Alexandra Kuo[4], Magdaline Asewe[3], Stephen Gakuo[2], Hilma N. Nakambale[4], Melissa Mugambi[4], Andy Stergachis[4], Josephine Odoyo[3], Elizabeth A. Bukusi[3], Kenneth Ngure[2], Jared Baeten[4]

*[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]Partners in Health Research and Development, Thika, Kenya, [3]Kenya Medical Research Institute, Kisumu, Kenya, [4]University of Washington, Seattle, WA, USA*

**Background:** The delivery of oral HIV pre-exposure prophylaxis (PrEP) at retail pharmacies has the potential to overcome existing barriers to clinic-delivered PrEP services, including HIV-associated stigma, long wait times, and understaffing. We pilot tested a model of pharmacy-based PrEP initiation and refills in Kenya – the first of its kind in sub-Saharan Africa.

**Methods:** At five retail pharmacies (two in Kisumu and three in Thika) we piloted a model of pharmacy-based PrEP delivery developed in collaboration with Kenyan stakeholders (CT.gov: NCT04558554). In this model, pharmacy providers (pharmacists and pharmaceutical technologists) asked clients purchasing services potentially indicating HIV risk (eg, emergency contraception, STI treatment) if they might be interested in PrEP for HIV prevention. These providers screened interested clients for HIV risk (using Kenya's Rapid Assessment Screening Tool), counseled them on PrEP safety, tested them for HIV using oral-fluid self-tests, and prescribed and dispensed PrEP with support from a remote clinician for clinically-challenging cases. Pharmacy providers were permitted PrEP prescribing authority for the pilot, and no additional staff provided PrEP care. PrEP supply was dispensed for one month at initiation and three months thereafter.

**Results:** From November 2020 to October 2021, we screened 575 clients accessing services associated with HIV risk at retail pharmacies and initiated 287 (49%) on PrEP. Two-thirds (387/575) of clients screened reported a sexual partner of unknown HIV status, and 63% (362/575) reported inconsistent condom use. Among clients initiating PrEP, the median age was 26 years (IQR 22-33), 43% (124/287) were female, and 38% (108/287) were married. Most clients learned of pharmacy PrEP from the pharmacy provider (42%, 121/287) or via informal word-of-mouth referral (43%, 123/287). PrEP continuation was 54% (155/287) at one month, 35% (92/267) at four months, and 32% (29/92) at seven months.

**Conclusion:** Pharmacy-based PrEP delivery, conducted entirely by private-sector retail pharmacy staff, is a feasible new delivery model that has the potential to expand PrEP reach and access in Kenya and similar settings. Findings from this pilot suggest that populations at HIV risk frequently visit retail pharmacies and that PrEP initiation and continuation at pharmacies is similar to or exceeds that at clinics. More research is needed on the effectiveness of and costs associated with this novel model of PrEP delivery to inform scale up.

**929 COST-EFFECTIVENESS OF A COLLABORATIVE DATA-TO-CARE INTERVENTION FOR HIV PREVENTION**

**Ram Shrestha**[1], Robyn Fanfair[1], Liisa Randall[2], Crystal Lucas[3], Lisa Nichols[4], Nasima Camp[1], Kathleen Brady[3], Heidi Jenkins[5], Frederick Altice[4], Alfred DeMaria[2], Merceditas Villanueva[4], Paul Weidle[1]

*[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, [2]Massachusetts Department of Public Health, Boston, MA, USA, [3]Philadelphia Department of Public Health, Philadelphia, PA, USA, [4]Yale University, New Haven, CT, USA, [5]Connecticut Department of Public Health, Hartford, CT, USA*

**Background:** Data-to-care programs utilize surveillance data to identify persons who are out of HIV care, re-engage them in care, and improve HIV care outcomes.

**Methods:** The Cooperative Re-engagement Control Trial (CoRECT) employed a data-to-care collaborative model between health departments and HIV care providers. The health departments in Connecticut (CT), Massachusetts (MA), and Philadelphia (PHL) collaborated with HIV clinics to identify newly out-of-care patients and randomize them to receive usual linkage and engagement in care services (standard-of-care control arm) or health department-initiated active re-engagement services (intervention arm). We used a microcosting approach to identify the activities and resources involved in the CoRECT intervention and quantified the labor and non-labor costs. The cost data were collected at start-up and recurrent phases of the trial to incorporate potential variation in the intervention costs. We estimated costs and cost-effectiveness of re-engagement in care for each project site from the health care provider perspective.

**Results:** The CoRECT trial in CT, MA and PHL randomly assigned on average 327, 315, and 305 participants per year either to the intervention arm (n=166, 159, and 155) or the standard-of-care arm (n=161, 156, and 150), respectively. Of those randomized, the number of participants re-engaged in care within 90 days in the intervention and standard-of-care arms were 85 and 67 in CT, 84 and 69 in MA, and 98 and 64 in PHL. The additional number of participants re-engaged in care in the intervention arm compared with those in the standard-of-care arm was 18 (CT), 15 (MA), and 34 (PHL). We estimated annual total intervention cost at $490,040 in CT, $473,297 in MA, and $439,237 in PHL. The average cost per participant enrolled was $2,952, $2,977, and $2,834, and the average cost per participant re-engaged in care was $5,765, $5,634, and $4,482 in CT, MA, and PHL, respectively. We estimated an incremental cost per participant re-engaged in care at $27,224 (CT), $31,553 (MA), and $12,919 (PHL).

**Conclusion:** The costs of the collaborative re-engagement in HIV care intervention are comparable with other similar interventions, suggesting a potential for its cost-effectiveness. Further analysis may account for site-specific variation in program implementation and cost sharing between health department and clinics.

**930 COGNITIVE BEHAVIORAL THERAPY FOR HIV & DEPRESSION: COST-EFFECTIVENESS IN SOUTH AFRICA**

New Investigator Scholar

**Aditya R. Gandhi**[1], Emily P. Hyle[1], Justine Scott[1], Jasper S. Lee[2], Fatma M. Shebl[1], John Joska[3], Lena S. Andersen[3], Conall O'Cleirigh[1], Steven A. Safren[2], Kenneth Freedberg[1]

*[1]Massachusetts General Hospital, Boston, MA, USA, [2]University of Miami, Miami, FL, USA, [3]University of Cape Town, Cape Town, South Africa*

**Background:** Depression affects 25–30% of people with HIV (PWH) in South Africa (RSA) and is associated with antiretroviral therapy (ART) nonadherence and increased mortality. We evaluated the cost-effectiveness of an 8-session cognitive behavioral therapy (CBT) intervention that improved clinical outcomes in a recent randomized controlled trial for PWH diagnosed with depression and first-line virologic failure in RSA.

**Methods:** Using the Cost-Effectiveness of Preventing AIDS Complications microsimulation model, we simulated two treatment strategies: 1) Enhanced treatment as usual (ETAU), a nurse-led evaluation of depression with referral to the participant's HIV provider, and 2) ETAU plus 8 weekly CBT sessions focused on ART adherence and depression (CBT-AD). Cohort characteristics included mean initial age (39y; standard deviation [SD]: 9y) and CD4 count (214/μL; SD: 182/μL). We modeled the monthly probability of HIV mortality (0.002–0.095), CD4-stratified quality-of-life estimates for untreated depression (0.64–0.68) and CBT-treated depression (0.80–0.86), and costs of ART ($6–22/month) and CBT ($29/session). We calibrated to viral suppression at one year in the trial: 20% (ETAU) versus 32% (CBT-AD). Beyond one year, we projected 5y and 10y viral suppression, life expectancy, lifetime costs, and incremental cost-effectiveness ratios (ICERs: $/QALY [quality-adjusted life-year], discounted 3%/year). Based on a recent RSA economic threshold study, we considered a strategy cost-effective if its ICER was ≤$2,545/QALY [0.5x annual per capita GDP in RSA]. We conducted sensitivity analyses to determine how input parameter variation affected model results.

**Results:** Model-projected 5y/10y viral suppression was 18.9%/8.7% (ETAU) compared with 21.1%/9.7% (CBT-AD) (Table). Compared with ETAU, CBT-AD would increase discounted life expectancy from 4.12 to 4.68 QALYs and discounted lifetime costs from $6,210/person to $6,610/person, resulting in an ICER of $730/QALY. The only scenarios where CBT-AD was not cost-effective (ICER >$2,545/QALY) occurred when CBT-AD improved one-year viral suppression by <2% and also cost ≥$75/session.

**Conclusion:** An 8-session CBT intervention for PWH with depression and virologic failure in RSA is projected to improve life expectancy and be cost-effective. CBT-style interventions should be integrated into HIV care in South Africa and other low-/middle-income settings with high burdens of HIV and depression.

Table. Projected clinical, cost, and cost-effectiveness outcomes of an 8-week cognitive behavioral therapy intervention (CBT-AD) and status-quo treatment (ETAU) for people with HIV with depression and first-line virologic failure in South Africa

| Strategy | Viral suppression [a] | | Life expectancy [b] | | Per-person lifetime costs [b] | | ICER [c] |
|---|---|---|---|---|---|---|---|
| | 5y | 10y | undiscounted | discounted [d] | undiscounted | discounted [d] | |
| | % | % | *QALYs* | *QALYs* | *2020 USD* | *2020 USD* | *$/QALY* |
| **ETAU** | 18.9 | 8.7 | 5.15 | 4.12 | 7,560 | 6,210 | Comparator |
| **CBT-AD** | 21.1 | 9.7 | 5.85 | 4.68 | 8,120 | 6,610 | 730 |

[a] Viral suppression is defined as an HIV RNA <20 copies/mL or "undetectable." Results represent the number of people with HIV alive and virologically suppressed at the designated time point divided by the initial population size.
[b] Life expectancy is rounded to the nearest 0.1 year, and per-person costs are rounded to the nearest $10.
[c] ICER: the difference in cost divided by the difference in discounted life expectancy of one strategy compared with the next less costly strategy. ICERs summarize the degree to which an intervention provides benefit relative to its cost (i.e., cost-effectiveness). We considered an ICER ≤$2,545/QALY (0.5x annual *per capita* 2020 RSA GDP) to be cost-effective.
[d] Results are discounted 3%/year.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; USD, United States dollars; ETAU, enhanced treatment as usual; CBT-AD, cognitive behavioral therapy for adherence and depression.

## 931 AGRICULTURAL LIVELIHOOD INTERVENTION REDUCES HIV STIGMA: RESULTS FROM A CLUSTER RCT

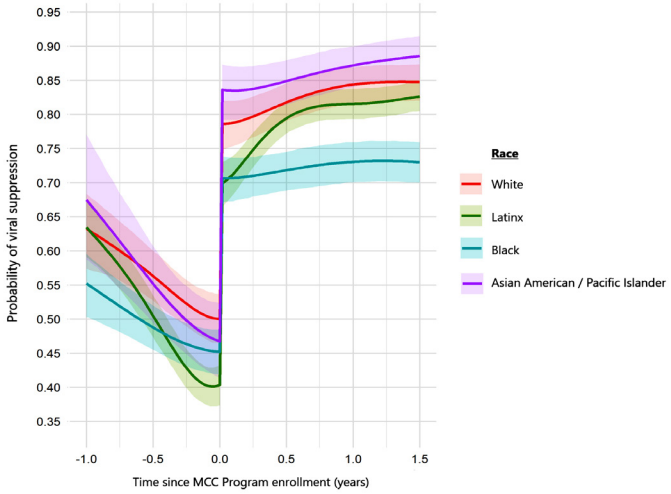
**Sheri D. Weiser**[1], Edward A. Frongillo[2], Adrienne R. Mocello[1], Elly Weke[3], Lila A. Sheira[1], Rachel L. Burger[1], Pauline Wekesa[3], Harsha Thirumurthy[4], Shari Dworkin[5], Lisa Butler[6], Alexander C. Tsai[7], Elizabeth A. Bukusi[3], Craig R. Cohen[1]
*[1]University of California San Francisco, San Francisco, CA, USA, [2]University of South Carolina at Columbia, Columbia, SC, USA, [3]Kenya Medical Research Institute, Nairobi, Kenya, [4]University of Pennsylvania, Philadelphia, PA, USA, [5]University of Washington Bothell, Bothell, WA, USA, [6]University of Connecticut, Storrs, CT, USA, [7]Massachusetts General Hospital, Boston, MA, USA*

**Background:** HIV stigma poses a significant barrier to successful antiretroviral treatment (ART) adherence and viral suppression, particularly in sub-Saharan Africa. Livelihood interventions could potentially reduce stigma by weakening symbolic associations between HIV and economic incapacity and premature morbidity. We examined the effects of a multisectoral agricultural livelihood intervention on internalized, anticipated, and enacted stigma among people living with HIV (PLHIV) on ART in Western Kenya.
**Methods:** Sixteen health facilities were randomly allocated (1:1) to intervention or control arms in Shamba Maisha, a cluster RCT which aimed to improve HIV health through behavioral, mental health and nutritional paths. The intervention included a loan to purchase farming implements (including a human-powered water pump, seeds, and fertilizers) and training in sustainability farming practices and financial management. Participants were included if they were ≥18 years old, on ART >6 months, moderately-to-severely food insecure, and had access to farmland and surface water. We interviewed participants semiannually at clinic and home visits for two years. We measured HIV-related stigma across three domains: internalized, anticipated, and enacted stigma, using validated Likert scales consisting of 6-9 questions each; each scale score ranged from 1 (lowest) to 5 (highest). We compared changes in scores between baseline and endline at 24-months by arm by employing longitudinal multi-level difference-in-difference linear regression models accounting for clustering of facilities using the intention-to-treat cohort.
**Results:** We enrolled 720 participants (354 intervention, 366 control); two-year retention was 94%. Median age was 40 (interquartile range 34, 47), and 55% of participants were female. In comparison to the control arm, the intervention resulted in greater decreases of 0.417 points in internalized stigma ($p<0.001$), 0.426 points in anticipated stigma ($p<0.001$), and 0.127 points in enacted stigma ($p<0.001$) arm over the 24-month study period. These relationships held for each sex in stratified analyses.
**Conclusion:** An agricultural livelihood intervention reduced internalized, anticipated, and enacted stigma among PLHIV on ART. These results point to a novel strategy for reducing HIV stigma by targeting some of the core drivers of negative attitudes towards PLHIV.

## 932 PSYCHOSOCIAL FACTORS INTERACT WITH RACE DURING COUNTYWIDE PERSONALIZED HIV CARE

**Michael** J. **Li**[1], Brendon Chau[1], Wendy Garland[2], Sona Oksuzyan[2], Robert E. Weiss[1], Sae Takada[1], Uyen Kao[1], Sung-Jae Lee[1], Steve Shoptaw[1]
[1]**University** of California Los Angeles, Los Angeles, CA, USA, [2]Los Angeles County Department of Public Health, Los Angeles, CA, USA

**Background:** Black and Latinx people in the United States are disproportionately affected by the HIV epidemic, driven by structural and social factors. In Los Angeles County (LAC), California, Black and Latinx people living with HIV (PLWH) experience high rates of new diagnoses and low levels of engagement in care and viral suppression (VS, <200 c/mL) compared to other racial groups. The LAC Department of Public Health (DPH) implemented a countywide Medical Care Coordination (MCC) Program in 2013 to provide integrated medical and psychosocial case management to PLWH with complex needs. We report a longitudinal evaluation of MCC that compares trajectories of VS by gender and race, while accounting for differences in psychosocial issues.
**Methods:** We analyzed VS data from 10,455 PWH in the LA County MCC from 12m prior to MCC enrollment to 18m post-enrollment. Baseline psychosocial acuity (PSA) measured housing need, socioeconomic status, mental health, social environment, substance use, and sexual risk behaviors with higher scores indicating someone with greater psychosocial needs. We used Bayesian longitudinal modeling to estimate the change in probability of VS over time as a function of race/ethnicity (White, Latinx, Black, and Asian American/Pacific Islander (AAPI), gender (cisgender male, cisgender female, and transgender female), and PSA.
**Results:** Overall, MCC patients had a greater probability of VS by 6-18m after MCC enrollment (82%) compared to the 12m leading up to enrollment (43-62%). Cisgender male, cisgender female, and transgender female patients in MCC achieved and sustained similar probabilities of VS from 6m-18m post-enrollment. By 6m following MCC enrollment, Black patients had lower probability of VS (72%) than White, Latinx, and AAPI patients (79-85%). By 18m post-enrollment, Black patients did not achieve the same probability of VS (74%) as the other racial groups (83-87%). When accounting for interaction by PSA, Black patients with high PSA had similar levels of VS as patients from other racial/ethnic groups with high PSA (50-55%) by 18m post-enrollment. In contrast, Black patients with low PSA had lower levels of VS (79%) than the other racial groups with low PSA (88-95%).
**Conclusion:** Future evaluation is needed to understand the differential impact of structural and social factors for Black PLWH that may impede access to care and successful treatment to reduce disparate health outcomes and advance the national Ending the HIV Epidemic Initiative.




## 933 MENTAL HEALTH AND PrEP ADHERENCE AMONG MSM/NON-CISGENDER PEOPLE FROM LATIN AMERICA

**Hamid Vega-Ramirez**[1], Centli Guillén-Díaz-Barriga[1], Dulce Diaz[1], Kelika A. Konda[2], Thiago S. Torres[3], Oliver A. Elorreaga[2], Brenda Hoagland[3], Juan V. Guanira[2], Marcos R. Benedetti[3], Sergio Bautista-Arredondo[4], Beatriz Grinsztejn[3], Carlos F. Caceres[2], Valdilea Veloso[3]
*[1]National Institute of Psychiatry Ramón de la Fuente Muñiz, Mexico City, Mexico, [2]Universidad Peruana Cayetano Heredia, Lima, Peru, [3]Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, [4]Instituto Nacional de Salud Pública, Mexico City, Mexico*

**Background:** Pre-exposure prophylaxis (PrEP) is an effective HIV prevention strategy among men who have sex with men (MSM) and trans women. Mental health well-being and substance use decrease adherence to antiretroviral treatment among people living with HIV, but their role in PrEP adherence is still unclear. We sought to assess the association of mental health well-being, depression, substance use, and other characteristics with self-reported PrEP adherence.
**Methods:** This is a secondary analysis of an online survey conducted from May to August 2021 in Brazil, Mexico, and Peru where the willingness to use different PrEP modalities was explored. We used a subsample of daily PrEP (d-PrEP) users and assessed sociodemographic data, mental health well-being and depression scores, sexual behavior, alcohol use, and substance use. Participants were

≥18 years, MSM or non-cisgender people who gave their informed consent. Adherence to d-PrEP was evaluated based on self-report number of pills taken per week in the last month and them dichotomized into two groups: perfect adherence (7 pills/week) and non-perfect (<7 pills/week). We used the SF-36 and the PHQ-2 to assess mental health well-being and depression scores, respectively. We performed simple logistic regressions with each variable and kept the significant ones (P<0.1) to develop a final multivariate logistic model.

**Results:** Out of our sample of 1,415 d-PrEP users, 1,313 completed the questionnaire. The median age was 34 (IQR: 29-40), 87.1% were from Brazil, 10.3% from Mexico and 2.6% from Peru, the majority were MSM (98.3%) and had more than secondary education (79.9%). Perfect adherence to d-PrEP was reported by 93.2% of the participants, 23% were classified as depressed, and the median mental health score was 21 (IQR: 17-24). Overall, perfect adherence to d-PrEP was associated with higher mental health well-being score, higher numbers of sexual partners, and regular use of geosocial networking apps. On the other hand, depression and having a stable partner decreased the odds of perfect d-PrEP adherence. Nevertheless, after the adjusted model only having a stable partner and high number of sexual partners remain associated with perfect d-PrEP (Table 1).

**Conclusion:** The role of depression and mental health well-being on PrEP adherence is still unclear, but behavioral/relational variables (i.e. having a steady partner; numbers of partners) are associated with d-PrEP adherence.

**Table 1. Factors associated with daily PrEP adherence among men who have sex with men and non-cisgender people from Brazil, Mexico, and Peru.**

| | Perfect adherence (n= 1,223) n (%) | Non-perfect adherence (n= 90) n (%) | OR (95% CI) | P | AOR (95% CI) | P |
|---|---|---|---|---|---|---|
| Age 18-24 *(vs. 25+)* | 83 (6.8) | 10 (11.1) | 0.58 (0.29 – 1.17) | 0.127 | -- | -- |
| >Secondary education *(ref. ≤secondary)* | 978 (80) | 71 (78.9) | 1.07 (0.63 – 1.81) | 0.805 | -- | -- |
| Country *(ref. Brazil)* | | | | | | |
| *Mexico* | 125 (10.2) | 10 (11.1) | 0.89 (0.45 – 1.76) | 0.738 | -- | -- |
| *Peru* | 30 (2.5) | 4 (4.4) | 0.53 (0.18 – 1.55) | 0.250 | | |
| Depression *(yes)* | 273 (22.3) | 29 (32.2) | 0.60 (0.38 – 0.96) | **0.033** | 0.71 (0.40 – 1.27) | 0.250 |
| Subjective well-being: median (IQR) | 21 (17-25) | 19 (16-24) | 1.05 (1.01 – 1.10) | **0.012** | 1.05 (1.00 – 1.11) | 0.054 |
| Stable partner *(yes)* | 376 (30.7) | 40 (44.4) | 0.55 (0.36 – 0.86) | **0.008** | 0.61 (0.38 – 0.99) | **0.044** |
| Use of GSN apps *(ref. never)* | | | | | | |
| *Sometimes* | 873 (72.6) | 57 (64.8) | 2.04 (1.10 – 3.79) | **0.024** | 1.14 (0.55 – 2.36) | 0.719 |
| *Daily* | 222 (18.5) | 17 (19.3) | 1.74 (0.83 – 3.67) | 0.144 | 0.95 (0.41 – 2.19) | 0.904 |
| Number of sexual partners *(ref. ≤5)* | | | | | | |
| *6-10* | 240 (20) | 18 (20.5) | 1.42 (0.80 – 2.51) | 0.228 | 1.34 (0.74 – 2.42) | 0.337 |
| *>10* | 546 (45.5) | 26 (29.5) | 2.24 (1.36 – 3.69) | **0.002** | 2.11 (1.23 – 3.61) | **0.007** |
| Condomless anal sex *(yes)* | 1,092 (89.3) | 78 (86.7) | 1.28 (0.68 – 2.42) | 0.442 | -- | -- |
| Sex under alcohol intoxication *(yes)* | 548 (45.5) | 44 (50) | 0.84 (0.54 – 1.29) | 0.419 | -- | -- |
| Stimulant drug use *(yes)* | 351 (28.7) | 24 (26.7) | 1.11 (0.68 – 1.79) | 0.680 | -- | -- |

*GNS: geosocial networking; IQR: Interquartile range*

## 934 EFFECTS OF THE COVID-19 LOCKDOWN ON MENTAL HEALTH CARE USE IN PEOPLE LIVING WITH HIV

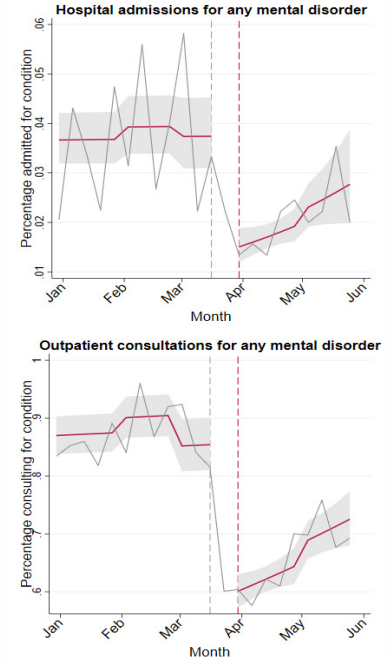
**Anja E. Wettstein**[1], Mpho Tlali[2], John Joska[3], Morna Cornell[2], Veronika W. Skrivankova[1], Soraya Seedat[4], Hannes Mouton[2], Leigh Van den Heuvel[4], Nicky Maxwell[2], Mary-Ann Davies[2], Gary Maartens[5], Matthias Egger[1], Andreas D. Haas[1]
*[1]Institute of Social and Preventive Medicine, Bern, Switzerland, [2]Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa, [3]HIV Mental Health Research Unit, Department of Psychiatry and Mental Health, Neuroscience Institute, Cape Town, South Africa, [4]Department of Psychiatry, Faculty of Medicine and Health Sciences, University of Stellenbosch, Cape Town, South Africa, [5]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa*

**Background:** Mental health complications are highly prevalent among people living with HIV. Left untreated mental health complications can negatively affect HIV treatment outcomes. In March 2020, South Africa introduced a lockdown in response to the COVID-19 pandemic. Lockdowns might induce or exacerbate mental health conditions and limit access to treatment. We studied the effect of the lockdown on mental health care use among HIV-positive beneficiaries of a South African private sector medical aid scheme.

**Methods:** We performed an interrupted time series analysis using insurance claims from January 1, 2017, to June 1, 2020 of HIV-positive beneficiaries aged 18 years or older from a large private sector medical aid scheme. Weekly outpatient consultation and hospital admission rates were calculated for substance use disorders (ICD10 F10-F19), serious mental disorders (F20-F29, F31), depression (F32, F34.1, F54), anxiety (F40-F48), and any mental disorder (F00-F99). We estimated adjusted odds ratios (OR) for the effect of the lockdown on weekly hospital admission and outpatient consultation rates.

**Results:** 61,873 adults living with HIV were followed up for a median of 151 weeks. Hospital admission rates (OR 0.38; 95% CI 0.27-0.54) and outpatient consultation rates (OR 0.72; 95% CI 0.64-0.82) for any mental disorder decreased substantially after the implementation of the lockdown in March 2020 and did not recover to pre-lockdown levels until June 1, 2020 (Figure). Substantial decreases were observed in hospital admissions rates for substance use disorders (OR 0.13; 95% CI 0.02-0.73), depression (OR 0.30; 95% CI 0.16-0.54), and serious mental disorders (OR 0.58; 95%CI 0.17-2.02). Decreases in outpatient consultation rates were observed for substance use disorders (OR 0.21; 95% CI 0.08-0.55), anxiety disorders (OR 0.64; 95% CI 0.54-0.76), depression (OR 0.71; 95% CI 0.62-0.82), and serious mental disorders (OR 0.85; 95% CI 0.72-1.00).

**Conclusion:** Reduced mental health care contact rates during the COVID-19 lockdown likely reflect a substantial unmet need for mental health services with potential long-term consequences for people living with HIV and comorbid mental health complications. Steps to ensure access and continuity of mental health services during future lockdowns should be considered.




## 935 CHARACTERISTICS OF DEATHS IN A PEPFAR HIV PROGRAM IN DEMOCRATIC REPUBLIC OF THE CONGO

**Dany Malaba**[1], Michelle Selim[2], Paola Chanes-Mora[2], Hilary T. Wolf[2]
*[1]US Department of State, Kinshasa, Congo, The Democratic Republic Of The, [2]US Department of State, Washington, DC, USA*

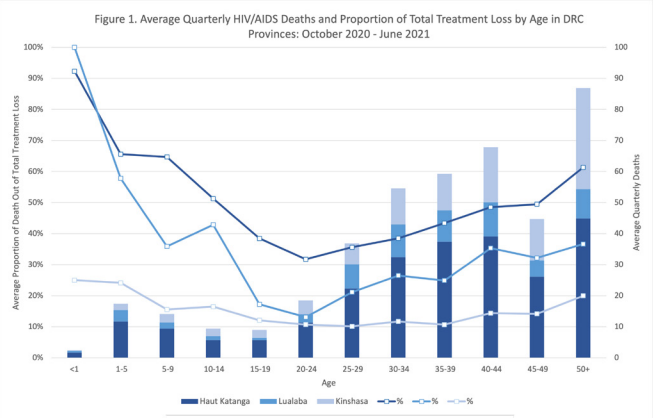
**Background:** The HIV epidemic in DRC is heterogenous, with an estimated 510,000 people living with HIV (PLHIV) in 2021. PEPFAR supports three high burden provinces, comprising of half the total number of PLHIV in DRC. We aimed to evaluate the proportion and characteristics of PLHIV who were lost from treatment and died in DRC PEPFAR programs.

**Methods:** We conducted an analysis using health services data from PEPFAR global and DRC Monitoring, Evaluation and Reporting (MER) of all instances of treatment loss among individuals on ART and were recorded as ''died'' between October 2020 to June 2021 (FY20Q1 to FY21Q3) within a cohort of 195,093 patients on treatment. Outcomes are stratified by geographic area, age, and sex. Quarterly average number of deaths are reported and outcomes are measured as an average proportion of total treatment loss.

**Results:** In DRC, there was an average of 1,525 treatment loss occurrences per quarter across the study period of which 421 average quarterly deaths were reported. This results in a quarterly mortality rate of 0.21% for the entire treatment cohort which is mid-range compared to other PEPFAR-supported countries. However, DRC has the second highest average proportion of deaths out of total treatment loss (28%) compared to other PEPFAR-supported countries (1%-29%). The average proportion of deaths was highest in Haut Katanga province (46%), where half of the treatment cohort resides, compared to Lualaba (28%) and Kinshasa (14%). Figure 1 shows the distribution of deaths by age and proportion of deaths out of total treatment loss. Within Haut Katanga, 50+ year olds had the highest number of average deaths per quarter reported followed by 40-44 year olds. In Haut Katanga, children under 10 experienced the highest average proportion of deaths out of total treatment loss compared to older age groups. Four urban (Kenya, Lubumbashi, Ruashi,

Kampemba) and one rural (Sakania) Haut Katanga health zones accounted for 50% of quarterly average deaths out of 26 health zones. Males (51%) had slightly higher average proportion of deaths compared to females (44%) out of total treatment loss in Haut Katanga.

**Conclusion:** While the mortality rate is mid-range in DRC for the treatment cohort, it is concerning that a high proportion of treatment loss in Haut Katanga were associated deaths. This analysis is limited by data completeness on treatment loss in DRC and globally. Further research is needed to better understand these findings to determine how to reduce mortality.




## 936 SURVIVAL AFTER HIV INFECTION IN THE ERA OF DECENTRALIZED DRUG DISTRIBUTION MODELS

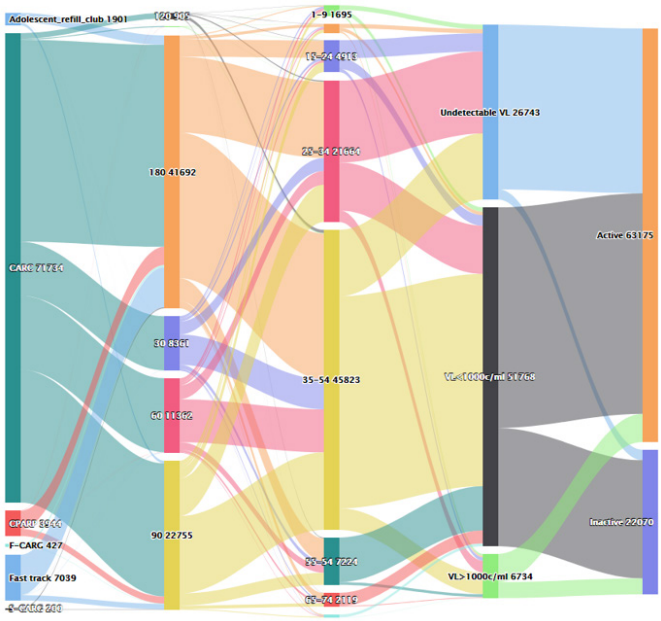
**Amobi Onovo**[1], David Onime[1], Jemeh Pius[1], Thomas Minior[2], Sena Woldetensay[2], Moses Katbi[1], Kalaiwo Abiye[1], Adeoye Adegboye[1], Onyeka Igboelina[1], Chika Obiora-Okafo[1], Helina Meri[1], Rachel Goldstein[1]
*[1]US Agency for International Development, Abuja, Nigeria, [2]US Agency for International Development, Washington, DC, USA*

**Background:** Since 2004, USAID Nigeria has supported the provision of antiretroviral therapy (ART) to 575,000 people living with HIV (PLHIV) in Nigeria through PEPFAR. Six decentralized drug distribution (DDD) ART delivery models were implemented in Akwa Ibom and Cross River states to improve continuous access to treatment for PLHIV, with the goal of achieving long-term retention in care and viral suppression.

**Methods:** A retrospective analysis of 85,245 treatment patients who began ART between October 2001 and December 2020 was conducted. Patient data was extracted from electronic record systems and anonymized. All patients on first-line ART were included. Retention was defined as being alive and remaining on ART after initiation for at least 12 months after starting ART. While eligibility to all DDD models was restricted to stable patients, Community Pharmacy ART Refills Program (CPARP), Community ART Refill Clubs (CARCs), Family-Centered ART Refills Groups (F-CARGs), Fast-track clinic, and Adolescents Refill Clubs (ARCs) were all expanded to include stable and unstable patients after the onset of COVID-19. The Self-forming Community ART Refill Groups (S-CARG) model remained open only to stable patients. The Kaplan-Meier method was used to estimate retention probabilities, and Cox Proportional Hazards model was used to examine factors associated with retention.

**Results:** Of the total sample, 63,175 (74%) remained on treatment and 13,800 (16%) experienced treatment interruption/LTFU. Median age at ART initiation was 39 years (IQR:32-47) and 69% of the cohort was female. Overall retention probability was 95%, 72% and 62% at 12, 24 and 36 months, respectively. The median retention time in the CPARP model was 73 months (95%CI: 71-74) compared to 49, 47, 18, 16, and 14 months in the CARC, Fast-track, ARC, F-CARG, and S-CARG models, respectively, log-rank test (p<.001). CARC DDD model [Hazard Ratio (HR):0.70 (0.66-0.73), ref: ARC], CPARP [HR:0.56 (0.53-0.60), ref: ARC], Fast-track [HR:0.70 (0.79-0.83), ref: ARC], female sex [HR:0.96 (0.94-0.97), ref: male], and 15+ years Age [HR:0.80 (0.77-0.84), ref: <15 years] were associated with long-term retention; while unemployed Occupation [HR:1.10 (1.08-1.13), ref: employed] and senior secondary Education [HR:1.20 (1.14-1.26), ref: junior secondary] were associated with short-term retention.

**Conclusion:** Decentralized Drug Delivery models were associated with improved rates of continuity of ART treatment in a large real-world cohort in Nigeria.




## 937 TELEMEDICINE AND HIV CARE QUALITY MEASURES DURING THE COVID-19 PANDEMIC

**Mary Clare C. Masters**[1], Juan Rivera[2], Mia Calamari[1], Katherine Wright[2], Patrick Janulis[1], Laura Rusie[2], Jacqueline Bannon1, Patrick Milne[1], Shannon Galvin[1], Elena Molina[2], Lisa R. Hirschhorn[1], Frank Palella[1], Rebecca N. Kumar[3], Cory Brown[2], Claudia Hawkins[1]
*[1]Northwestern University, Chicago, IL, USA, [2]Howard Brown Health Center, Chicago, IL, USA, [3]Georgetown University Medical Center, Washington, DC, USA*

**Background:** During the COVID-19 pandemic, HIV care providers urgently adopted telemedicine as an alternative to routine in-person person visits to ensure continuity of care. We examined how introducing televisits at a community and an academic outpatient HIV clinic during the COVID-19 pandemic affected technical quality of care for persons with HIV (PWH).

**Methods:** The study included all non-pregnant adult PWH who had at least two visits for HIV care in the 18 months prior to 3/13/2020 at the Howard Brown Health Centers (HB) and Northwestern University Infectious Disease Center (NU-IDC) and in Chicago, Illinois. HIV care quality indicators (described in Table) were calculated using data extracted from electronic medical records during 4 different time periods: 1. pre-pandemic (1/1/19-3/1/2020), 2. early pandemic (7/1/2019-9/1/2020), 3. mid-pandemic (1/1/2020-3/1/2021), and 4. current (7/1/2020-9/1/2021). Measures were compared between intervals 2-4 and interval 1 (pre-pandemic) using generalized linear mixed models to estimate differences in indicators across intervals within each site while controlling for multiple observations of individuals. Differences by age group, race, and sex at birth were also compared.

**Results:** 6,447 PWH were included in the analysis. The proportion of televisits peaked between April-June 2020 (71-75% at HB 53-89% at NU-IDC) then declined by July-September (33-35%at HB, 10-15% at NU). Changes in quality care measures are shown in Table 1. There were significant declines in care utilization and disease monitoring measures in intervals 2,3 &4 compared to interval 1. The largest declines were observed in STI screening. Measures of HIV virologic suppression, BP control, and HbA1C <7% (in both persons with and without diabetes) were stable with no significant differences noted in these measures between interval 4 and 1. Similar trends were observed across all age, race and sex subgroups.

**Conclusion:** During the COVID-19 pandemic and rapid implementation of televisits, indicators of care utilization and disease monitoring decreased compared to pre-pandemic levels. Despite these reductions, proportions with virologic, BP, and glycemic control remained stable among PWH. The effect of televisits as well as other patient factors on HIV quality indicators and their changes over time during COVID-19 need to be further examined.

Table. Indicators (%) by site and intervals.

| | Howard Brown Health | | | | Northwestern | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| **Utilization** | | | | | | | | |
| Virtual or in-person provider encounter in the last 8 months | 89.0 | 74.6* | 69.8* | 68.1* | 94.3 | 85.3* | 81.7* | 78.8* |
| **Monitoring** | | | | | | | | |
| HIV VL measurement | 90.7 | 82.2* | 72.1* | 73.8* | 92.1 | 85.4* | 73.4* | 74.5* |
| BP measurement | 92.9 | 80.40* | 52.7* | 59.9* | 97.5 | 70.6* | 74.2* | 78.2* |
| HbA1C measurement (persons with diabetes) | 65.5 | 45.3* | 60.2 | 58.8* | 57.8 | 46.7* | 53.8 | 51.8 |
| HbA1C measurement (persons without diabetes) | 11.8 | 8.0* | 16.6* | 19.3* | 34.1 | 32.6* | 30.1* | 29.4* |
| Mammogram | 11.0 | 4.6* | 3.7* | 7.3 | 36.7 | 29.7 | 30.7 | 0 |
| STI screening | 91.2 | 82.1* | 70.8* | 72.6* | 61.9 | 55.9* | 51.6* | 47.9* |
| **Disease Control** | | | | | | | | |
| HIV VL <50 | 82.9 | 83.8* | 85.0* | 86.1* | 90.6 | 92.3* | 88.6* | 90.8 |
| BP control | 83.3 | 81.8* | 80.0* | 83.3 | 61.7 | 61.9 | 59.3* | 63.8 |
| HbA1C <7% (persons with diabetes) | 47.3 | 47.6 | 48.2 | 48.3 | 61.7 | 61.3 | 68.2 | 65.1 |
| HbA1C <7% (persons without diabetes) | 78.8 | 78.2 | 86.0 | 87.8 | 88.0 | 87.9 | 90.0* | 86.8 |

Note: HIV viral load (VL) measurement, suppressed VL, blood pressure (BP), controlled BP (<140/90), and STI screening (≥1 of syphilis serology, urine, rectal or oro-pharyngeal chlamydia/Gonorrhea PCR) were included for prior 12 months. Hemoglobin A1C (HbA1C) level measurement and control (<7%) were included in the last 12 months for persons without diabetes and the last 6 months for persons with diabetes. Mammogram was included the last 12 months for women >50.
*Indicate p < 0.05 in comparison to interval 1 (pre-pandemic)

## 938 DID COVID-19 RESTRICTIONS IMPACT HIV TREATMENT AMONG MSM IN CHINA?

New Investigator Scholar

**Yinghui Sun**[1], Weiran Zheng[1], Hui Li[2], Yanxiao Gao[3], Yuewei Zhan[3], Hui Chen[4], Yong Cai[4], Huachun Zou[3]

*[1]Sun Yat-sen University, Guangzhou, China, [2]Shizhong District Center for Disease Control and Prevention, Jinan, China, [3]Sun Yat-sen University, Shenzhen, China, [4]Shanghai Jiao Tong University, Shanghai, China*

**Background:** Travel restrictions during the COVID-19 epidemic in China have impacted on the daily life and antiretroviral therapy (ART) of people living with HIV, including men who have sex with men (MSM). As China enters a state of routine COVID-19 prevention and control, it is necessary to understand the conditions of ART interruption (ATI) among HIV-infected MSM during and after the lockdown period (23 January to 7 April 2020) to summarize experience on HIV treatment.

**Methods:** A nationwide cross-sectional online survey was conducted among HIV-infected MSM in China in February 2021, using convenience sampling on the WeChat platform called Li Hui Shi Kong. We collected information during and around lockdown period, including socio-demographics, health behaviors such as physical exercise and alcohol drinking, ART maintenance, CD4 and viral load testing. Pearson's Chi-squared test was performed to compare those characteristics between participants who experienced ATI during the lockdown period and did not. Logistic regression analysis was conducted to assess the correlates of ATI.

**Results:** A total of 1296 participants were included in the analysis. The median age was 29.3 years (interquartile range [IQR] 25.2-34.0). 40.9% (n=530) of them did not exercise regularly in the second half of 2019 and 62.3% (n=808) had alcohol drinking. During the lockdown period, 6.8% (n=88) reported ATI experience, and 49.5% (n=629) performed CD4 cell test. Among the participants who took the last CD4 test after the lockdown, more people had not experienced ATI (66.8%) compared to those had experienced ATI (38.6%). HIV-infected MSM using other ART regimen as temporary substitution were more unlikely to experience ATI, including free ART (adjusted odds ratio [aOR] 0.05, 95% confidence interval [CI] 0.02-0.11) and out-of-pocket ART (aOR 0.11, 95% CI 0.01-0.89), which is different from their previous prescription.

**Conclusion:** COVID-restrictions did not result in significantly negative effects on ART maintenance among HIV-infected MSM in China. In order to reduce the negative impact on HIV-infected MSM, attention should be paid to conducting health behavior education, maintaining ART service and encouraging CD4 and viral load testing during and after public emergencies.

## 939 PANDEMIC ERA CHANGES IN HIV/STI DIAGNOSES AND PrEP USE IN AN URBAN US HEALTH CENTER

**Kenneth H. Mayer**[1], Sy Q. Gitin[1], Douglas Krakower[2], Chris H. Grasso[1], Katie Biello[3]

*[1]Fenway Health, Boston, MA, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]Brown University, Providence, RI, USA*

**Background:** The SARS-CoV-2 pandemic affected care for HIV+ and at-risk persons. The current analyses assess whether the recent Delta Surge (DS) had an impact comparable to the initial pandemic at a Boston community health center (CHC) specializing in HIV care and prevention.

**Methods:** The analyses divided the periods of observation by quarter, comparing the prevalence of HIV and STI tests performed, test positivity, new HIV diagnoses and PrEP starts during 3 quarterly periods: Pre-Pandemic (PP, 12/1/19-2/28/20), Early Pandemic (EP, 3/1/20-5/31/20); DS (6/1/21-8/31/21). Comparisons were made using Student's t tests for means and chi-square tests for proportions.

**Results:** The quarterly N of HIV tests decreased from 5,047 in PP (monthly average=1685) to 1,734 in EP (monthly average=575; p=.017), but increased to 3,973 during the DS (monthly average=1342) (p for EP vs. DS=.037). Although the monthly average of new HIV diagnoses did not significantly decline between PP and EP (7.0 vs. 3.7, p=.206), they increased to a monthly average of 17 during DS (p for EP vs. DS=.031). Virologic suppression rates remained stable, ranging from 92.1% during PP to 90.1% in the EP (p=.375), but rose to 93.6% during DS (p=.032). Total PrEP starts (new and restarts) decreased significantly between PP and EP (monthly average: 176 vs. 91, p=.017), but rebounded during the DS (monthly average=227, p=.233 compared to PP); however, restarts were 63.3% of all PrEP starts during DS compared to only 38.6% PP (p<.00001). Race and ethnicity of patients starting PrEP did not differ across the three periods; however, those who started PrEP during the DS were older (mean=37.1) than those in PP and EP (mean=33.5 and 34.3 respectively, p<.001). The mean number of syphilis, gonorrhea (GC) and chlamydia (CT) tests performed monthly dramatically decreased during EP compared to PP (p=0.01) with a rebound approaching PP levels during DS (p=0.045). Syphilis test positivity rates tended to remain at similar levels throughout the pandemic (p=0.5), but GC/CT positivity increased significantly during EP (p<0.0001), but returned to PP levels during the DS (p=0.476).

**Conclusion:** The onset of the SARS-CoV-2 pandemic was initially asscociated with major decreases in HIV/STI testing, diagnoses, and PrEP starts in a Boston CHC, but by the DS, rates of HIV/STI screening, test positivity, new HIV diagnoses, and PrEP starts/restarts increased, suggesting sexual risk behavior, as well as engagement in care were approaching or exceeding pre-pandemic levels.

**Trends in Monthly Numbers of HIV, PrEP and STI Measures in Boston Community Health Center During the Pandemic**

| | Pre-Pandemic[1] | Early Pandemic (p vs. pre-pandemic) | Delta Surge (p vs. pre-pandemic) |
|---|---|---|---|
| HIV tests, mean | 1685.0 | 575.3 (0.017) | 1342 (0.061) |
| New HIV diagnoses, mean | 7.0 | 3.7 (0.206) | 17.0 (0.093) |
| PVL performed, mean | 336.3 | 145.3 (0.007) | 253.7 (0.013) |
| Virally suppressed, % | 92.1 | 90.1 (0.227) | 93.6 (0.233) |
| PrEP restarts, mean | 68.0 | 47.3 (0.071) | 144.0 (0.068) |
| New PrEP starts, mean | 108.0 | 61.0 (0.014) | 83.3 (0.047) |
| GC/CT NAAT tests, mean | 7110.3 | 2422.0 (0.012) | 5670.0 (0.045) |
| GC/CT test positivity, % | 3.1% | 4.4% (<0.0001) | 3.3% (0.476) |
| syphilis tests, mean | 2029.0 | 699.7 (0.010) | 1592.3 (0.038) |
| Syphilis seropositivity, % | 2.0% | 1.76% (0.518) | 1.8% (0.478) |

[1]Pre-pandemic quarter: 12/19-2/20; Early pandemic quarter: 3/20-5/20; Delta surge quarter: 6/21-8/21.

## 940 COVID-19–RELATED DISRUPTIONS IN THE HIV CARE CONTINUUM IN A LARGE URBAN COHORT OF PWH

**Amanda Castel**[1], Shannon K. Barth[1], Michael A. Horberg[2], Jiayang Xiao[1], Anne Monroe[1], Alan E. Greenberg[1]

*[1]George Washington University, Washington, DC, USA, [2]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA*

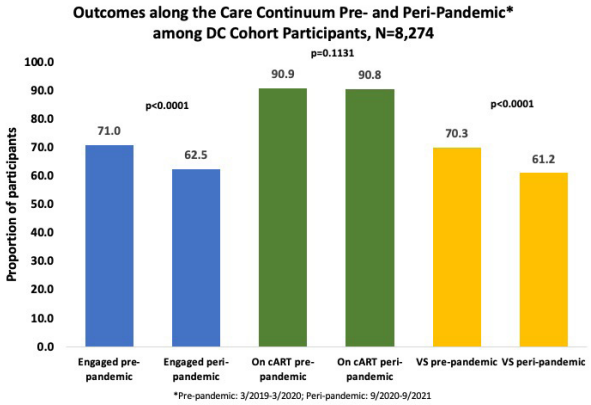
**Background:** COVID-19 has caused severe disruptions in healthcare access. The impact on persons with HIV (PWH), including their outcomes along the HIV care continuum is still being assessed. Washington, DC is a hotspot for both HIV and COVID-19 infections. We sought to describe the impact of COVID-19 on the care continuum among a cohort of PWH enrolled in a longitudinal HIV study, the DC Cohort.

**Methods:** DC Cohort participants enrolled by 09/1/2018 and active as of 3/1/2020 were included in the analysis (N=8,274). Using cross-sectional and longitudinal approaches, we assessed engagement in care (EIC) (i.e., at least one viral load [VL], CD4 or visit), receipt of cART, and viral suppression (VS)(i.e., VL<200 copies/ml) during the pre-pandemic era (3/1/2019-3/1/2020) versus the recent peri-pandemic era (9/1/2020-9/1/2021) using Cohort data. A subset of participant data was linked to a cross-sectional COVID-19 survey (N=801). Uni- and bivariate analysis were used to describe care continuum outcomes and factors associated with care disruption.

**Results:** Among 8,274 participants, engagement in care during the pre (71.0%) vs peri pandemic (62.5%) era declined significantly (p<.0001). The proportion of participants who were on cART during each era was stable (90.9% vs 90.8% respectively, p=0.1131). 70.3% of participants achieved VS in the pre pandemic era vs 61.2% in the peri-pandemic era (p<.0001). Longitudinally, 9.5% of participants were no longer EIC peri-pandemic; 2.4% of participants were no longer on cART peri-pandemic, 6.5% had a loss of VS and 7.3% had no labs in the peri-pandemic era. Among the subset of participants completing the survey,

there were no significant differences between those who maintained VS versus those who did not/had no labs in demographics, employment, changes in income, insurance or housing, or self-reported ability to access non-HIV related care or telehealth. Most surveyed participants reported no change in their ability to fill ARV prescriptions (86%) or daily ARV adherence (89%); however, 20% and 13% reported decreased ability to make and keep HIV appointments, respectively, and 15% reported decreased ability to get laboratory examinations completed.

**Conclusion:** Our analysis shows that COVID-19 has disrupted HIV care continuum outcomes including EIC, ART, and loss of viral suppression. As the pandemic continues, efforts to engage PWH through telehealth, multi-month dispensing, and home-based testing, are needed to ensure continued progress towards ending the HIV epidemic.




## 941 SARS-CoV-2 VACCINATION: IMPACT ON HIV-1 RNA LEVELS AND ANTIBODY RESPONSE AMONG PLWH

**Vera Portillo**[1], Pilar Ustero[1], Chiara Fedeli[1], Ianis Petignat[1], Ellen Cristina Mereles Costa[1], Adi Sulstarova[1], Cyril Jaksic[1], Sabine Yerly[1], Alexandra L. Calmy[1]
[1]*Geneva University Hospitals, Geneva, Switzerland*

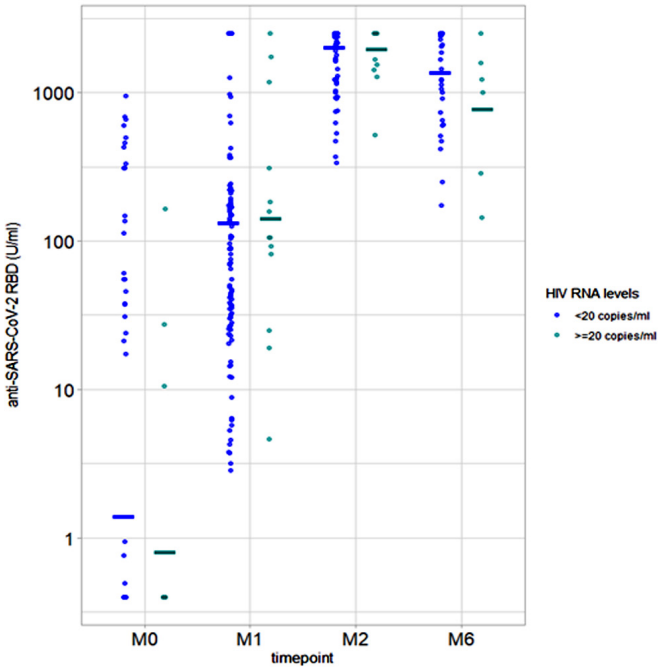
**Background:** The immunogenicity and safety of mRNA-based vaccination in people living with HIV have yet to be clarified. We aimed to describe the impact of SARS-CoV-2 mRNA vaccination on safety, HIV-RNA control, and humoral immune responses after two doses of vaccine.

**Methods:** From January 2021 to April 2021, vaccination with mRNA1273 (Moderna) and BNT162b2 (BioNTech/Pfizer) was offered to every individual with HIV registered at our institution who fulfilled vaccination criteria and consented to routine vaccination. HIV-1 RNA levels and anti-SARS-CoV-2 S total Ig (Elecsys®, Roche Diagnostics, Rotkreuz, Switzerland) were measured at the time of the first and second doses, 30 days later, and at 6 months after the first dose.

**Results:** The study sample included 131 individuals (median age: 54 years [interquartile range (IQR): 47-60.5]); male: 70.2%; median baseline CD4-T cell: 602 cells/µl [IQR: 445.0-825.5]). HIV viral load data were collected for 129 patients at the time of the first dose (M0) and 30 days later (M1); for 124 patients, 30 days after the second dose (M2); and for 42 patients, 6 months after the first dose (M6). Twenty (15.5%) of 129 patients had detectable HIV-1 RNA (>20 copies/ml; IQR: 24.0-43.5) at M0, 13/129 (10.1%) at M1 (among which 5 were newly detected), 15/124 (12.1%) at M2 (among which 4 were newly detected), and 6/42 (14.3%) at M6. HIV-RNA levels returned below the detection threshold of 20 copies/mL at the subsequent measure. All analyzed patients showed a positive anti-SARS-CoV-2 S Ig after vaccination with geometric mean titers (GMT) of 131.8 U/ml (95% CI: 130.4-133.2) 30 days after the first dose and 2003.4 U/ml (95% CI: 2002.3-2004.4) 30 days after the second dose. Six months after the first dose, 75/131 patients were analyzed, and they were all still positive for anti-SARS-CoV-2 S Ig, with GMT of 1132.2 U/ml (95% CI: 1131.0-1133.4). We found no statistical significance in anti-SARS-CoV-2 S Ig titers between patients with detectable and undetectable HIV-1 RNA. No serious adverse effects were reported.

**Conclusion:** In a patient population on effective antiretroviral drugs, only minor or transient effects of mRNA vaccines on HIV-1 RNA levels were observed. All patients developed anti-SARS-CoV-2 S total antibodies after two-dose vaccination and antibodies were detectable in all analyzed patients 6 months after the first dose.

**Figure 1**. anti-SARS-CoV-2 S titers (GMTs) in patients who developed blips (green dots) or not (blue dots) at baseline (M0), 30 days after the first dose (M1), 30 days after the second dose (M2), and 6 months after the first dose (M6).




## 942 IMPACT OF COVID OUTBREAK ON PREVENTION AND CARE FOR HIV AND STIs AT A LARGE HOSPITAL

**Esteban Martinez**[1], Elisa de Lazzari[1], Ivan Chivite[1], Ana Gonzalez-Cordon[1], María M. Mosquera[1], Montserrat Laguno[1], Jordi Bosch[1], Jose L. Blanco[1], Miriam Alvarez-Martinez[1], Berta Torres[1], Juan C. Hurtado[1], Josep Mallolas[1], Jose M. Miro[1], Maria A. Marcos[1]
[1]*Hospital Clinic of Barcelona, Barcelona, Spain*

**Background:** Routine medical care was drastically affected by the overwhelming irruption of COVID-19 pandemic. We comprehensively assessed the impact of the COVID-19 pandemic on the prevention and care for HIV and other sexually transmitted infections at a large reference hospital providing preventive and clinical services for HIV infection and other sexually transmitted infections.

**Methods:** We retrospectively compared clinical and laboratory data from March to December 2020 (first ten months of the SARS-CoV-2 epidemics in Spain) vs. the same period 2019 in the setting of Hospital Clínic of Barcelona which provides preventive and clinical services for HIV infection and other sexually transmitted infections for the region of Catalonia and is the largest of its kind in Spain. Monthly clinical data on HIV pre-exposure and post-exposure prophylaxis users and on adults with HIV infection were retrieved from the administrative hospital database. Monthly tests for HIV, hepatitis B and C, Treponema pallidum, Neisseria gonorrhoeae, and Chlamydia trachomatis, and plasma lipids and glucose were recovered from the laboratory database. De novo HIV, hepatitis B, or hepatitis C diagnosis were considered whenever a person had a first known positive laboratory test.

**Results:** There were less (28% reduction) but more advanced (mean [SD] CD4 cell counts per $mm_3$ at HIV diagnosis 305 [167] vs. 370 [170], P<0.001; 26 (18%) persons had AIDS-defining conditions at HIV diagnosis vs. 20 (10%), P=0.03) HIV cases and more gonorrhea (39% increase, P<0.001) and chlamydia (37% increase, P<0.001) infections in 2020 vs. 2019. In people with HIV, rates of viral load above the level of detection remained stable (11% vs 11%, P=0.147) despite less scheduled visits (25% reduction, P<0.001). However, they had less antiretroviral prescription changes (10% reduction, P=0.018), worse plasma lipids (mean total cholesterol 190 vs 185 mg/dL, P<0.001; mean LDL cholesterol 114 vs 110 mg/dL, P<0.001; mean triglycerides 136 vs 125 mg/dL, P<0.001; mean HDL cholesterol 47 vs 48 mg/dL, P=0.006), and an excess of mortality (29 deaths vs 11, 264% increase, P=0.006) due in great part to COVID-19 (n=11) but also to other non-COVID-19 causes.

**Conclusion:** In the setting of a large Spanish reference hospital, SARS-CoV-2 epidemics was associated with an increase of some prevalent sexually

transmitted infections, with less but more advanced de novo HIV infections, and with worse non-virologic healthcare outcomes and higher mortality in people living with HIV.

## 943 CHARACTERIZING THE SCOPE AND DRIVERS OF THE IMPACT OF COVID-19 ON LOCAL HIV EPIDEMICS

**Anthony T. Fojo**[1], Emma Wallengren[2], Melissa Schnure[2], Ruchita Balasubramanian[2], David Dowdy[2], Maunank Shah[1], Parastu Kasaie[2]
*[1]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*

**Background:** The potential impact of COVID-19 pandemic on the US HIV epidemic remains unclear. Characterizing the scope and main drivers of the impact of COVID-19 on HIV incidence can inform future HIV policy.
**Methods:** We characterized the impact of COVID-19 pandemic and attendant lockdowns on HIV epidemiology via reductions in sexual transmission (0–50%) from March 1st, 2020 to July 4th, 2021, plus reductions in viral suppression (0–40%), HIV testing (0–50%), and pre-exposure prophylaxis use (0–30%) from March 1st to February 4th, 2022. Using the Johns Hopkins Epidemiologic and Economic Model (JHEEM) of HIV transmission, we projected HIV infections from 2020 to 2025 across 32 high-priority US cities and compared these to projections if COVID-19 had not emerged.
**Results:** Across all 32 cities, 80% of simulations projected a decline in HIV incidence in 2020 (median decrease of 15% from 2019), before rebounding in 2021 (96% of simulations, median increase of 13% from 2020) – see Figure, panel B. Projections of the impact of the COVID-19 pandemic on cumulative HIV incidence from 2020-2025 varied by city, ranging from a median of 3% fewer incident cases in Las Vegas to 9% more incident cases in Boston (Figure, panel A). At the MSA level, reductions in sexual transmission had the strongest impact on incidence, followed by reductions in viral suppression. Among simulations that incorporated large (>25%) reductions in viral suppression due to COVID-19, adverse impacts on HIV incidence were greater where pre-pandemic levels of viral suppression were higher (ranging from a median 1% increase in cumulative incidence 2020-25 in Chicago with 52% pre-pandemic suppression, to a 24% increase in Seattle with 86% pre-pandemic suppression – Figure, panel C).
**Conclusion:** The effects of COVID-19 on HIV transmission remain uncertain and differ substantially at the local level. Disruptions to HIV care and viral suppression due to the COVID-19 pandemic may have greater impact in increasing HIV incidence in settings where pre-existing suppression levels are higher.

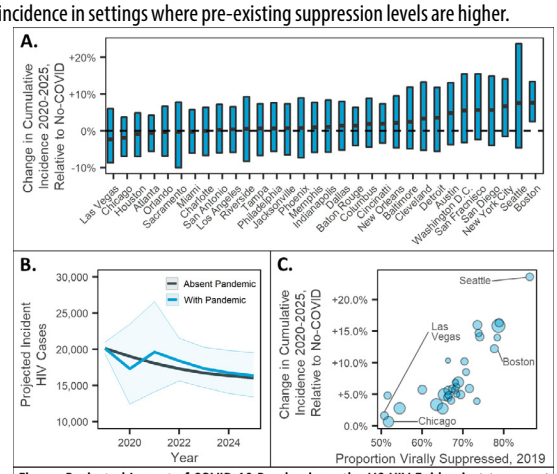



**Figure: Projected Impact of COVID-19 Pandemic on the US HIV Epidemic.** (A) Projected impact of pandemic on incidence in 32 US cities (horizontal lines denote the median, boxes denote the 50% credible interval). (B) Projected total HIV incidence across all cities (C) Relationship between pre-pandemic level of viral suppression and impact of the pandemic on HIV incidence, in simulations with large (>25%) reductions in viral suppression due to the pandemic. Circles represent individual cities; the size of each circle is proportional to the city's 2019 incidence.

## 944 HEALTHCARE ACCESS AMONG SOUTH AFRICAN YOUTH LIVING WITH & WITHOUT HIV DURING COVID-19

New Investigator Scholar

**Danielle Giovenco**[1], Audrey Pettifor[2], Stephanie Chung[2], Gina Itzikowitz[3], Yamkela Qayiya[3], Linda-Gail Bekker[3]
*[1]Brown University, Providence, RI, USA, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]Desmond Tutu HIV Foundation, Cape Town, South Africa*

**Background:** We aimed to examine concerns surrounding COVID-19 infection and healthcare access among South African young people (YP) living with HIV (YPLWH) and HIV-uninfected YP with the goal of identifying differences between groups.
**Methods:** We examined cross-sectional data from the baseline procedures of the BUDDY study conducted among YP (13-24 years) living with and without HIV in Cape Town, South Africa from February – September 2021. YPLWH were recruited from an HIV clinic and HIV-uninfected YP were recruited through community outreach. Adjusted prevalence ratios (aPRs) were computed to estimate associations between HIV cohort and COVID-19 testing, vaccine acceptance, and access to healthcare services since March 2020 controlling for participant age and gender.
**Results:** A total of 535 participants were enrolled into the study, including 217 YPLWH and 318 HIV-uninfected YP. The median age, 19.1 years (IQR=16.6-21.5), was similar between groups. YPLWH were 58% female and HIV-uninfected YP were 78% female (p<.001). YPLWH were less than half as likely than HIV-uninfected YP to have received a COVID-19 test (6% vs 12%, aPR=0.48, 95% CI 0.26-0.89), to be willing to accept a COVID-19 vaccine (49% vs 59%, aPR=0.84, 95% CI 0.71-0.99), and to be concerned about becoming severely ill from COVID-19 (60% vs 76%, aPR=0.79, 95% CI 0.69-0.89). Perceived risk of becoming infected with COVID-19 in the next month was similar between YPLWH and HIV-uninfected YP (32% vs 36%). YPLWH were more likely than HIV-uninfected YP to report being unable to attend a healthcare appointment (27% vs 20%, aPR=1.39, 95% CI 1.01-1.90). Further, a greater proportion of YPLWH attempted to access condoms (aPR=1.51, 95% CI 1.32-1.74) and HIV/STI testing services (aPR=1.58, 95% CI 1.38-1.80) than HIV-uninfected YP and, among females who attempted to access contraceptives services, YPLYW reported significantly lower access than HIV-uninfected YP (aPR=0.82, 95% CI 0.71-0.94) (Table 1). Last, among YPLWH, 28% reported missing an HIV care appointment, 14% reported running out of their HIV medication, and 34% reported they were worried about running out of their medication since March 2020.
**Conclusion:** Experiences living with HIV may shape concerns around COVID-19 infection among YP. YPLWH reported greater health-seeking behavior than HIV-uninfected YP and a significant proportion reported missing an appointment and running out of their HIV medication. Services should devise strategies to prevent interruptions in healthcare access among YP.

Table 1. Access to sexual and reproductive health (SRH) services among young people (YP) living with HIV (YPLWH) and HIV-uninfected YP since March 2020

| | YPLWH (N = 217) | HIV-uninfected YP (N = 318) | Chi-square |
|---|---|---|---|
| **SRH service access** | N (%) | N (%) | p-value |
| Unable to access contraceptives (girls only) | 19 (15.2) | 13 (5.4) | |
| Able to access contraceptives (girls only) | 57 (45.6) | 131 (54.4) | |
| Not applicable (did not attempt to access/girls) | 49 (39.2) | 97 (40.2) | 0.006 |
| Unable to access condoms | 22 (10.2) | 11 (3.5) | |
| Able to access condoms | 113 (52.6) | 90 (28.9) | |
| Not applicable (did not attempt to access) | 80 (37.2) | 210 (67.5) | <.001 |
| Unable to access HIV/STI testing | 17 (7.9) | 11 (3.5) | |
| Able to access HIV/STI testing | 155 (72.1) | 142 (45.5) | |
| Not applicable (did not attempt to access) | 43 (20.0) | 159 (51.0) | <.001 |

## 945 COVID-19 AND THE HIV CARE CONTINUUM IN C3PNO COHORTS

**Catherine R. Lesko**[1], Jeanne C. Keruly[2], Richard Moore[2], Nikki Shen[1], Jarratt D. Pytell[3], Bryan Lau[1], Anthony T. Fojo[2], Shruti H. Mehta[1], Michele Kipke[4], Marianna K. Baum[5], Steve Shoptaw[6], Pamina M. Gorbach[6], Brian Mustanski[7], Marjan Javanbakht[6], Geetanjali Chander[2]
*[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3]John H Stroger Jr Hospital of Cook County, Chicago, IL, USA, [4]University of Southern California, Los Angeles, CA, USA, [5]Florida International University, Miami, FL, USA, 6University of California Los Angeles, Los Angeles, CA, USA, [7]Northwestern University, Chicago, IL, USA*

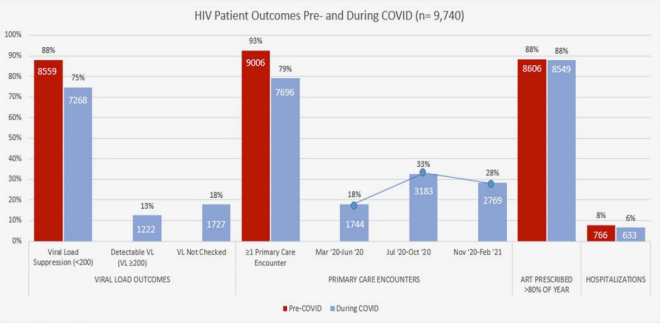
**Background:** The COVID-19 pandemic disrupted the normal delivery of HIV care, altered social support networks, and caused economic insecurity. People with HIV (PWH) are vulnerable to such disruptions, particularly if they have a history of substance use. We describe engagement in care and adherence to antiretroviral therapy (ART) for PWH during the pandemic.
**Methods:** From May 2020 to February 2021, 773 PWH enrolled in 6 existing cohorts completed 1495 surveys about substance use and engagement in HIV care during the COVID-19 pandemic. We described the prevalence and correlates of having missed a visit with an HIV provider in the past month and having missed a dose of ART in the past week.
**Results:** Thirteen percent of people missed an HIV visit in the past month. Missing a visit was associated with unstable housing, food insecurity, anxiety, low resiliency, disruptions to mental health care, and substance use including cigarette smoking, hazardous alcohol use, cocaine, and cannabis use. Nineteen percent of people reported missing at least one dose of ART in the week prior to their survey. Missing a dose of ART was associated with being a man, low

resiliency, disruptions to mental health care, cigarette smoking, hazardous alcohol use, cocaine, and cannabis use, and experiencing disruptions to substance use treatment.
**Conclusion:** Social determinants of health, substance use, and disruptions to mental health and substance use treatment were associated with poorer engagement in HIV care. Close attention to continuity of care during times of social disruption is especially critical for PWH.

## 946 IMPACT OF THE COVID-19 PANDEMIC ON HIV OUTPATIENT CARE AND VIRAL SUPPRESSION IN NYC

**Shaoli Chaudhuri**[1], Judith A. Aberg[1], Rachel Chasan[1], Emma Kaplan-Lewis[2], Keith Sigel[1]
*[1]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [2]New York City Health + Hospitals, New York, NY, USA*

**Background:** The COVID-19 pandemic has had significant impacts on the healthcare system, including HIV outpatient care. Lockdowns, infection concerns, and staffing and resource shortages had the potential to affect patient care and viral suppression.
**Methods:** We conducted a retrospective analysis of patients at six HIV primary care clinics in New York City in the Mount Sinai Health system. We compared outcomes in a pre-COVID period [PC], Mar 2019-Feb 2020, to a COVID period [CP] of Mar 2020-Feb 2021. Demographics of interest included age, sex, race/ethnicity, and HIV risk factor. In the two time periods we compared viral load suppression (VLS; HIV RNA <200 copies/mL), primary care encounters, antiretroviral (ART) prescribing, and hospitalizations. We then evaluated predictors of loss of VLS or loss to follow-up in a logistic regression model.
**Results:** Our cohort was comprised of 9,740 HIV primary care patients with ≥1 viral load measurement PC. Median age was 53 years and 79% were male; 20% were white, 37% Black, and 30% Hispanic. 42% had an HIV risk factor of MSM, 22% heterosexual sex, and 4% injection drug use (IDU). 87.9% (8559/9740) of the PWH during PC had VLS. While 90.7% (7268/8013) of the population assessed during CP had VLS, 18% of the initial cohort had no VL testing during this period and 15% had neither testing nor a clinical visit during CP. In CP, 13% had at least one measured detectable HIV VL (≥200 copies/mL). Primary care encounters decreased from 93% to 79%. ART prescription rates were unchanged: 88% had active prescriptions for >80% of the year both PC and in CP. All-cause hospitalizations decreased from 766 (7.9%) to 633 (6.5%; p<.001). Male sex (OR 1.32,CI 1.17-1.49), identification as a transgender woman (OR 1.81,CI 1.22-2.69), age <35 years (OR 1.74,CI 1.53-1.97), Black race (OR 1.4,CI 1.23-1.59), and HIV risk factor of heterosexual sex (OR 1.54,CI 1.34-1.77) and IDU (OR 1.73,CI 1.35-2.22) were associated with loss of VLS or loss to follow-up.
**Conclusion:** In this large cohort of PWH in a NYC medical system, viral suppression of those who remained in care remained stable-yet a substantial portion of patients were not engaged in care and monitored for VLS during the CP. Strategies to retain patients in care and ensure suppression (eg, with televisits and care coordination) may have helped mitigate effects of the pandemic. Clinics must continue targeted efforts to re-engage patients, facilitate access to testing, and prevent longstanding loss to follow-up in at-risk groups.




## 947 THE IMPACT OF THE COVID-19 LOCKDOWN ON HIV CARE CONTINUUM IN CHINA

New Investigator Scholar

**Xinsheng Wu**[1], Ganfeng Luo[1], Yuanyi Chen[1], Yi-Fan Lin[1], Yiguo Zhou[1], Yanxiao Gao[1], Yuewei Zhan[2], Huachun Zou[1]
*[1]School of Public Health, Sun Yat-sen University, Shenzhen, China, [2]Shenzhen People's Hospital, First Affiliated Hospital of Southern University of Science and Technology, Shenzhen, China*

**Background:** China implemented strict lockdowns to contain COVID-19 at the early stage. We aimed to evaluate the impact of COVID-19 on HIV care continuum in China.
**Methods:** Anonymized programmatic data on HIV care continuum between 1 January 2017 and 31 December 2020 were collected from seven provincial and municipal centers for disease control and prevention and eight major infectious disease hospitals specialized in HIV care in various regions in China. We performed interrupted time series analysis to characterize temporal trend in monthly numbers of HIV tests, HIV diagnosis, HIV antiretroviral therapy (ART) initiations, ART collections, and HIV post-exposure prophylaxis (PEP) prescriptions before, during and after the national lockdown period (23 January to 7 April 2020). We used Poisson segmented regression models to estimate the immediate impact of the lockdown on these outcomes, as well as post-lockdown trends.
**Results:** During the study period, we recorded 1,101,686 HIV tests, 69,659 HIV diagnoses, 63,458 ART initiations, 1,593,490 ART collections, and 16,780 PEP prescriptions. A median of 789 (IQR 367-975), 409 (278-626), and 1045 (524-1262) HIV tests per day were recorded before, during and after lockdown. Lockdown was associated with 32.8% decrease in HIV testing in January 2020, the first month after lockdown (incidence rate ratio [IRR] 0.672; 95% confidence interval [CI] 0.585-0.772). Daily HIV diagnoses decreased from a median of 50 (7-76) before lockdown, to 23 (6-46) during lockdown, and back to 48 (12-74) after lockdown, with an estimated 27.1% decrease in January 2020 (0.729, 0.599-0.887). There was no marked change in the number of ART initiation and ART collection during the lockdown, but the number of ART collection was lower than the expected level by the end of December 2020 (0.761, 0.659-0.879). The number of monthly PEP prescriptions decreased significantly during the lockdown (0.362, 0.220-0.595) and still had not recovered to the expected level by the end of December 2020 (0.456, 0.362-0.574). With the ease of restrictions, HIV testing (slope change 1.067/month, 1.048-1.086) and PEP prescriptions (1.077/month, 1.016-1.142) showed a significant increasing trend.
**Conclusion:** ART initiation and ART collection generally remained stable during the lockdown, but HIV testing, HIV diagnosis and PEP prescription were affected. ART collection and PEP prescriptions have not recovered to expected levels in the eighth month after the suspension of lockdown.

## 948 COVID-19 PANDEMIC IMPACT ON HIV PrEP PROGRAM ENGAGEMENT IN BRITISH COLUMBIA

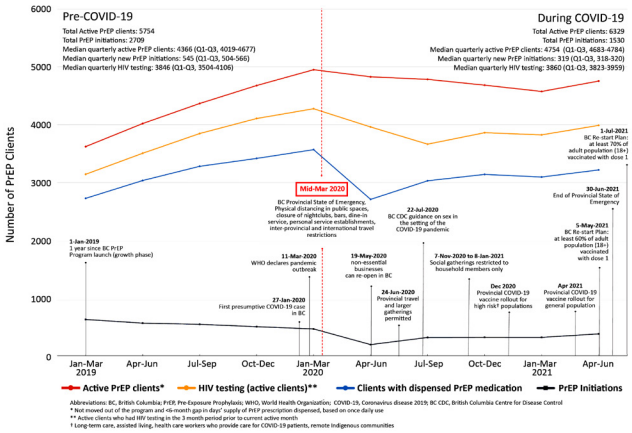
**Junine Toy[1],** Cora Keeney[1], Raquel M. Espinoza[1], Wendy Zhang[1], Diana Kao[1], Erin Ready[2], Jason Trigg[1], Katherine J. Lepik[1], Mark Hull[1], Taylor McLinden[1], Viviane D. Lima[1], Paul Sereda[1], David Moore[1], Rolando Barrios[1], Julio S. Montaner[1]
*[1]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada, [2]St. Paul's Hospital, Vancouver, Canada*

**Background:** In March 2020, British Columbia (BC) declared a COVID-19-related public health emergency. Measures to limit SARS-CoV-2 transmission impacted social behaviors and disrupted healthcare access. We examined client engagement in BC's province-wide, publicly-funded HIV PrEP program before and during the COVID-19 pandemic.
**Methods:** Using de-identified data from BC's provincial PrEP Program, we describe client engagement in the 15 months pre- (Jan 2019–Mar 2020) and during (Apr 2020-Jun 2021) the pandemic, summarized by 3-month periods. Fisher's exact, Wilcoxon rank sum test, and GEE models were used to compare median number of PrEP clients (total and new) and the proportion with PrEP dispensing and HIV testing in pre- vs during pandemic periods. We also compared these outcomes in the Apr-Jun quarter of 2019 (pre-) vs 2020 (early) and 2021 (late) pandemic.
**Results:** A total of 7300 clients engaged with the PrEP program during the 30-month study period, with median (Q1-Q3) age 33 (27-42) years, 98% cis-male, 1% trans-female, 98% gay-bisexual-MSM (gbMSM). The median (Q1-Q3) quarterly active PrEP clients increased from 4366 (4019-4677) pre-pandemic to 4754 (4683-4784) during-pandemic (p<0.001) following program expansion late 2019, but the median (Q1-Q3) number of new clients declined from 545

(504-566) to 319 (318-320; p=0.033) and the proportion of clients with HIV testing fell from 87% (87-88%) to 82% (77-82%; p<0.001). PrEP engagement in relation to the pandemic timeline (Figure) showed a transient, early pandemic drop in new initiations and medication dispensing followed by rebound. As a proportion of all active clients, new PrEP clients in the Apr-Jun quarter dropped from 14% in 2019 to 4% in 2020 (p<0.001) and remained lower at 8% in 2021 (p<0.001). A transient decrease in the proportion of new enrolees from sexual health clinics was also observed: 54% in 2019 to 44% in 2020 (p=0.017) with rebound to 55% in 2021 (p=0.784). Similarly, clients with PrEP dispensed in this quarter fell from 75% in 2019 to 56% in 2020 (p<0.001) with partial rebound to 68% in 2021 (p<0.001). HIV testing in PrEP clients fell from 87% in 2019 to 82% in 2020 (p<0.001) and remained lower at 84% in 2021 (p<0.001).

**Conclusion:** BC PrEP program engagement declined early in the COVID-19 pandemic, with partial rebound coinciding with the easing of public health restrictions. Ongoing clinical monitoring for PrEP remains key. Continued evaluation will facilitate understanding the pandemic impact on HIV prevention programming.

Figure: BC PrEP Program Engagement Before and During the COVID-19 Pandemic



# DISCLOSURE OF FINANCIAL RELATIONSHIPS WITH INELIGIBLE COMPANIES

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